

EXHIBIT 3

Marc J. Semigran, M.D.

June 23, 2010

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Volume: I
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Exhibits: See Index

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

MDL CASE NO. 2:09-cv-121
MDL 1968

IN RE: DIGITEK PRODUCT LIABILITY LITIGATION

* * * * *
BOBBY R. MILLIGAN, ET AL., :
PLAINTIFFS :
 :
v. :
 :
ACTAVIS GROUP HF, ET AL., :
DEFENDANTS :
* * * * *

DEPOSITION OF MARC J. SEMIGRAN, M.D., a witness
called on behalf of the Defendant, Actavis Group, HF,
pursuant to the provisions of the Federal Rules of
Civil Procedure, before Lisa McDonald Valdario, (CSR
#130093), a Registered Professional Reporter and
Notary Public in and for the Commonwealth of
Massachusetts, held at the Holiday Inn Boston at
Beacon Hill, 5 Blossom Street, Boston, Massachusetts
02114, on Wednesday, June 23, 2010, commencing at
10:04 a.m.



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1 I N D E X

2 WITNESS DIRECT CROSS REDIRECT RECROSS

3 MARC J. SEMIGRAN, M.D.

4 BY MR. MORIARTY 4 125

5 BY MS. DOWNIE 116

6 BY MR. MILLER 127

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8

9 E X H I B I T S

10 No. Description Page

11 43(A) Notice of Taking Deposition 4

12 43(B) Article: Relationship of Serum Digoxin 104
13 Concentration to Mortality and Morbidity
14 in Women in the Digitalis Investigation
15 Group Trial16 38 Document: Facts and Myths about Generic 112
17 Drugs

18 ***EXHIBITS GIVEN TO REPORTER TO APPEND TO

19 TRANSCRIPTS***

20

21

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24

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1 P R O C E E D I N G S

2 (Notice of Deposition marked Defendant

3 Exhibit No. 43(A) for identification.)

4 MARC J. SEMIGRAN, M.D.

5 A witness called for examination, having been

6 duly sworn, testified as follows:

7 DIRECT EXAMINATION

8 BY MR. MORIARTY:

9 Q Tell us your full name, please.

10 A Marc Semigran, Marc J. Semigran.

11 Q You are a cardiologist, aren't you?

12 A Correct.

13 Q First thing I want to hand you is Defendant's

14 Exhibit 43(A). This is a Notice of your

15 Deposition. Have you seen that before?

16 A Yes.

17 Q All right. And included in here was our request

18 that you bring certain documents, and I have

19 looked through here and I know some of these you

20 have, but I want to ask about some others.

21 Have you brought all correspondence and

22 communication between yourself and anyone

23 representing the plaintiffs in this litigation?

24 A Yes. Yes, I have.

25 Q That's in that manila folder you let me look

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1 through?

2 A Yes.

3 Q Any documents that the plaintiffs' attorneys
4 prepared and gave you, did you bring those?

5 A Yes.

6 Q Some billing information, did you bring that?

7 A Yes.

8 Q And then, of course this is your entire file, and
9 you've told me that you brought that, right?

10 A Yes.

11 Q And the documents that you reviewed, like medical
12 literature, you brought that?

13 A Yes. There's two that were very large that I
14 reviewed on line that I can transmit to you
15 electronically. They were each over 150 pages.
16 I'll be happy to do that.

17 Q Tell me what those were.

18 A Those were the Poison Control reports, I think
19 referenced in my statement.

20 Q Actually, I believe I retrieved those myself. I
21 created a binder, and I'm opening the binder to
22 Tab 8. You're talking about a document that looks
23 something like that?

24 A Yes.

25 Q That's the 2006?

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1 A Yes.

2 Q And then my binder Tab 9, that's the 2007?

3 A Yes, that looks like the front page, yes.

4 Q That's the two long documents you looked at on
5 line that you did not bring.

6 MR. MILLER: Matt, just for the record, if
7 you could read the title of Tab 8 and Tab 9, I'd
8 appreciate it; keep the record clear.

9 Q 2006 Annual Report of the American Association of
10 Poison Control Centers' National Poison Data
11 System; is that right?

12 A Yes.

13 Q And Tab 9 was the same title but for 2007, and
14 this is designated as the 25th Annual Report; is
15 that correct?

16 A That's what you're reading, yes.

17 Q Well, that's what you looked at on line.

18 A I looked at on line, a portion of it.

19 Q Did you take any handwritten notes during your
20 review of this material?

21 A No.

22 Q All right. Then this has been marked as Exhibit
23 42. This is the actual report that you drafted
24 for purposes of this litigation, is it not?

25 A It does look like it, yes. I brought my own copy.

1 Q We'll get your folder back to you. The last page
2 of this, page 12, is what you call References,
3 correct?

4 A Right.

5 Q And there are 11 items listed on here?

6 A Correct.

7 Q And the Tabs 8 and 9 of my binder correspond with
8 items 8 and 9 of your reference list, is that
9 right?

10 A Yes.

11 MR. MORIARTY: Pete, while I'm thinking of
12 it, there is a stack of the Exhibits.

13 MR. MILLER: Okay. Thank you.

14 MR. MORIARTY: And if Meghan wants her own
15 stack, we seem to have hacked a few trees today.

16 MR. MILLER: That's fine.

17 MS. CARTER: I can always make copies.

18 Q How many times have you had your deposition taken
19 before?

20 A About three or four.

21 Q And were all of those in medical negligence cases?

22 A Yes.

23 Q Have you ever been sued yourself for medical
24 negligence?

25 A No.

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1 Q Have you reviewed the specific medical records for
2 any plaintiff in the Digitek litigation?

3 A I think there were two.

4 Q All right. Do you anticipate writing specific
5 reports for those two patients in the Digitek
6 litigation?

7 A I was not asked to, so I would say not. I don't
8 know.

9 Q Okay.

10 A Depends whether I'm asked.

11 Q Have you reviewed the reports of any other experts
12 in this case?

13 A No.

14 Q Not even Dr. Nelson, the pharmacologist who we
15 deposed in Cincinnati yesterday?

16 A I've not been provided with it, so no.

17 Q That's fine. Prior to this litigation, when do
18 you think was the last time you looked at the
19 Detailed Patient Labeling for either Lanoxin or
20 any of its generic counterparts?

21 A When did the litigation start?

22 Q Summer of 2008.

23 A So prior to summer of 2008.

24 Q You know what, let me withdraw that question.

25 A Okay.

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1 Q Do you know when you were first retained as an
2 expert on this?

3 A I believe it was in approximately mid 2009 that I
4 was asked to review a couple of cases.

5 Q Who's been your primary contact with the
6 plaintiffs?

7 A Carmen Scott.

8 Q Did you have any previous consulting relationship
9 with Carmen Scott or her law firm, Motley Rice?

10 A No, I don't believe so.

11 Q So she called you presumably out of the blue,
12 right?

13 A Yes.

14 Q And you agreed to look at some specific cases or
15 the picture overall?

16 A No, specific cases at the time.

17 Q In those specific cases, did you find that there
18 was, just so I know what those cases were, was
19 there a clinical diagnosis in the medical records
20 of those patients of digoxin toxicity?

21 A I don't recall because I didn't write a report, so
22 I didn't really retain anything on it. It was
23 really, I mean, I think I reported back to her on
24 these in summer/fall of 2009. I think I have some
25 of the invoices on those in the file there so I

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1 could give you the exact dates.

2 Q Do you remember -- go ahead.

3 A And I don't really remember the details of the
4 cases.

5 Q Do you remember even grossly whether you said, I
6 think you have a case or don't have a case in
7 these two particular cases?

8 A I don't. I don't.

9 Q All right. Well, anyway, before you were
10 consulted by Carmen Scott, when was the last time
11 you think you reviewed the Detailed Patient
12 Labeling for either Lanoxin or any of its generic
13 counterparts?

14 A Probably 2007, 2008.

15 Q And what would have been the circumstances to
16 cause you to look at the Detailed Patient Labeling
17 for a digoxin product?

18 A Probably to review the pharmacokinetics in an
19 unusual situation that I was giving a patient
20 digoxin for.

21 Q Just so we're clear on what Detailed Patient
22 Labeling is, I'm going to hand you what I've had
23 marked as Defendant's Exhibit 7. That should be
24 the Lanoxin labeling.

25 A This looks like it comes from the PDR.

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1 Q Well, what comes from the PDR is essentially what
2 is contained in the package insert, is that
3 correct?

4 A I'm not sure. I mean, we usually, I usually would
5 go on line to the manufacturer's site where
6 they'll have the package insert on, you know,
7 they'll say For Professionals on the site, and
8 then they'll have the package insert.

9 Q All right. But at least that looks like the PDR
10 version of the Lanoxin Detailed Patient Labeling?

11 A That's what it looks like, yes.

12 Q Do you know whether the PDR is a compendium of FDA
13 approved Detailed Patient Labeling?

14 A I don't know.

15 MR. MILLER: Let me see that.

16 MR. MORIARTY: It's in your stack, I
17 believe.

18 MR. MILLER: Oh, okay.

19 MR. MORIARTY: If it isn't, I'm happy to
20 show it to you.

21 MR. MILLER: You are correct. Thank you.

22 Q So once you were called upon to consult in this
23 litigation, did you go back and look at either the
24 Lanoxin label or the Digitek label?

25 A Did not.

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1 Q Before last night or this morning, had you ever
2 met in person either Mr. Miller or Ms. Carter
3 Johnson, Johnson Carter, sorry, or Carmen Scott?

4 A I had not met either of these two, no. And I
5 believe I met Miss Scott when she was passing
6 through town, perhaps early 2009 or mid 2009 when
7 she came through, and asked just if I was
8 interested in discussing digoxin toxicity. She
9 told me a little bit about the Digitek situation.

10 Q Okay. And other than people we've already talked
11 about, have you talked about this litigation with
12 anybody else?

13 A No.

14 Q Any pharmacology or pharmacokinetic personnel at
15 Massachusetts General Hospital?

16 A No.

17 Q Any other cardiologists at Mass. General?

18 A No.

19 Q Any residents or fellows at Mass. General?

20 A No.

21 Q Have you asked any of your residents or fellows to
22 undertake any research for you regarding digoxin
23 or Digitek?

24 A No.

25 Q This is Exhibit 43. That is the CV that I was

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1 provided a week or so ago, two weeks ago, whenever
2 it was.

3 A Okay.

4 Q Does that look like your up-to-date CV?

5 A It does.

6 Q All right. And it is 49 pages long, right?

7 A Okay. I guess so.

8 Q I think you'll find me to be fairly trustworthy,
9 okay.

10 A Okay.

11 Q I want to ask you some questions about your
12 background and your work.

13 A Okay.

14 Q Feel free to look at that if you need to, okay?

15 A Thank you.

16 Q Obviously, you're board certified as a
17 cardiologist, right?

18 A Correct.

19 Q Do you have any other board certifications other
20 than possibly internal medicine?

21 A Internal medicine, that would be it.

22 Q Anything else?

23 A No.

24 Q Did you do any other subspecialty training besides
25 cardiology?

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1 A No. I did sub-subspecialty training in heart
2 failure, and actually, the board exam for the
3 first time, it's being offered this fall.

4 Q There's going to be a heart failure board exam?

5 A Correct.

6 Q Did you write the exam?

7 A No.

8 Q Are you sitting for the exam?

9 A Yes.

10 Q Okay.

11 A I plan to.

12 Q Overall, tell me what your current professional
13 interest really is. I mean, are you primarily a
14 heart failure cardiologist?

15 A Yes.

16 Q And I would assume at an institution as large and
17 prestigious at Mass. General, there is a
18 considerable amount of subspecialty that goes on?

19 A Yes.

20 Q So there may be electrophysiology cardiologists
21 and some cardiologists who focus more on atrial
22 fibrillation, et cetera, correct?

23 A Yes.

24 Q And tell me the extent of your inter-reaction with
25 the transplant program.

1 A I direct the heart transplant program.

2 Q You do, okay. Is there a colleague on the
3 surgical side who is a co-director of that?

4 A Yes. And I'm actually the medical director and he
5 is the surgical director.

6 Q Who is the surgical director?

7 A Bruce Rosengard.

8 Q As the medical director of the transplant program,
9 what is your function?

10 A Well, I am responsible for the administration of
11 the cardiac transplant program, including leading
12 the meetings that we have on a regular basis to
13 discuss potential cardiac transplant recipients
14 and transplant patients.

15 I am responsible or share responsibilities
16 with the surgical director for reporting to the
17 government and to the United Network for Organ
18 Sharing, our statistics, and the details about our
19 program.

20 I certainly have clinical responsibilities.
21 I work with the patients and help care for them.
22 I supervise my colleagues in doing so, as well as
23 our nursing staff that does so.

24 Q Okay. That gives me a pretty good idea.

25 A That's most of it.

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1 Q All right. So I think what you were saying, you
2 didn't use the word list, but there is such a
3 thing called a transplant list, is there not?

4 A You mean the list of people awaiting transplants?

5 Q Correct.

6 A Okay, yes.

7 Q And in order to be on the transplant list, there
8 is, application's not the right word, but you have
9 to qualify to be on the list, correct?

10 A Well, we evaluate patients, and if we think that
11 they would benefit from cardiac transplantation,
12 we place them on the list.

13 Q Are you part of the screening process for that?

14 A Yes.

15 Q Is it still true that there are more people who
16 need heart transplants than there are available
17 hearts for transplant?

18 A Yes.

19 Q How many heart transplants a year does
20 Massachusetts General Hospital perform?

21 A It's varied a fair amount by year. I believe we
22 did 19 in 2009 and 28 in 2008; approximately 18 in
23 2007. I could get that information for you.

24 Q No, that's -- I could probably look it up.

25 A Yes.

1 Q And nationally, where do your statistics place you
2 as far as volume of heart transplants?

3 A In the middle, I would say. We're certainly not
4 the highest volume. I doubt we're in the top 10
5 or so. There are I think approximately 150
6 cardiac transplant centers in the U.S. There are
7 a fair number of centers that do fewer than 10 a
8 year. I'd say we're in the middle.

9 Q That's fine. Is the Brigham in Boston also a
10 heart transplant center?

11 A Yes.

12 Q Is that the only other one in Boston?

13 A No.

14 Q How many are there in Boston?

15 A Four.

16 Q Every once in a while this fan is going to kick on
17 so we may have to ask you to repeat.

18 A That's okay.

19 Q Do you have any special training in quality
20 control chemistry in the pharmaceutical industry?

21 A No.

22 Q Do you have any special training in the quality
23 assurance process of the pharmaceutical industry?

24 A No.

25 Q Do you have any special training or experience in

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1 the regulatory aspects of the pharmaceutical
2 industry?

3 A No.

4 Q Have you ever published on any of those subjects?

5 A No, I don't believe so.

6 Q From looking at your CV, you do participate in a
7 substantial number of clinical trials, do you not?

8 A Fair number.

9 Q Have you ever worked directly for a pharmaceutical
10 company; in other words, been an employee of a
11 pharmaceutical company?

12 A No.

13 Q Have you ever been an employee of the FDA?

14 A No.

15 Q Which journals do you routinely review and rely on
16 for your clinical practice for cardiology?

17 A There are a fairly large number. I think that --

18 Q Why don't you give me the top five.

19 A Top five. New England Journal of Medicine,
20 Circulation, Circulation Heart Failure, Journal of
21 American College of Cardiology, Journal of Heart
22 and Lung Transplantation.

23 Q Were you or Mass. General involved in the, any of
24 the three following trials I'm going to mention,
25 DIG, D I G?

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1 A No.

2 Q PROVED, which is all caps.

3 A No.

4 Q Or RADIANCE, which is all caps.

5 A No.

6 Can I just correct that? I can speak for
7 myself. I don't believe anyone else at our
8 hospital was, but I know for myself that I was
9 not.

10 Q All right. From time to time, do you check any
11 references to see if a particular drug that you
12 are prescribing or thinking of prescribing for a
13 patient will interact with other drugs?

14 A Yes.

15 Q What references do you typically check to evaluate
16 that situation?

17 A Well, I'll look at the prescribing information
18 that's on line.

19 Q Okay, on line.

20 A I'll look at the literature. I'll do a PubMed
21 search or an Orbit search to see if there is a
22 potential interaction there. There is actually a
23 Mass. General Pharmaceutical Information Service
24 that I can look for.

25 Q Is that proprietary to Mass. General?

1 A I think some of it is, and some of it links to
2 outside reference services. And then we have
3 clinical pharmacists that we can consult with.

4 Q Okay. So when you say on line, are you talking
5 again going to like the manufacturer's data?

6 A That's one of the options, yes. For example, the
7 prescribing information.

8 Q Okay. All right. So just for example, if you're
9 going to look at the prescribing information the
10 GSK has for Lanoxin, what actual, would you go to
11 GSK, would you go to Lanoxin?

12 A I'd go to GSK.com, and look and see if they have
13 a, they usually have an area for professionals,
14 and go to that, and they'll usually have a list of
15 the drugs that they sell, and you can go to the
16 site for that, and they'll usually have a variety
17 of options there.

18 Q Right.

19 A The other thing that I have done is I've gone to,
20 the FDA.gov has its list of approved labeling and
21 approved prescribing information for drugs, and
22 actually, I'd say I've probably done that more
23 recently than gone to the manufacturers' sites.

24 Q Okay. Any particular reason why?

25 A Well, I wanted the latest official information on

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1 some medications.

2 Q Other than what you had in medical school or in
3 your post-graduate training, do you have any
4 special training in epidemiology?

5 A I've gone to occasional courses that are given at
6 the hospital. I don't have any certificates of,
7 you know.

8 Q What about pharmacology.

9 A Well, I, you know, I started in the Ph.D. program
10 of pharmacology in medical school, so I actually
11 completed the first year course requirements in
12 pharmacology.

13 Q Was that at Harvard Medical School?

14 A Correct.

15 Q Or was that part of the joint program you did at
16 MIT?

17 A Well, they were all the same really. So the Ph.D.
18 would have been from Harvard.

19 Q Got it, okay.

20 A And the courses I think were all at Harvard, but I
21 am not completely certain of that. It was a
22 number of years ago.

23 Q All right. So you had one year of specialty
24 training, and was that -- I mean, obviously you
25 deal with it daily.

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1 A Right.

2 Q But no more special training than that one year?

3 A No more special training than that one year. I
4 did research in the laboratory in pharmacology for
5 a year as well.

6 Q Was any of that research devoted to digoxin?

7 A No.

8 Q Or any other cardiac glycoside?

9 A No.

10 Q Tell me what your current faculty positions are.

11 A I'm an associate professor of medicine at Harvard
12 Medical School.

13 Q Is that it?

14 A That's it.

15 Q Now, I assume that -- well, first of all, are
16 there any didactic classroom teaching associated
17 with that position?

18 A Yes. I give, and it's in the CV, the details, but
19 I give one or two lectures a year to, in the
20 medical school to the cardiovascular pathophys
21 course. There are more frequent lectures to the
22 house staff in, I guess you say classrooms, and to
23 our cardiology fellows.

24 Q Okay. And then obviously, you have clinical
25 teaching responsibilities where you're rounding

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1 with some number of people, right?

2 A Correct.

3 Q Did you ever do any study of the Mass. General
4 statistics to see if there was any spike in
5 diagnoses of digoxin toxicity in 2005, 6, 7 or 8?

6 A Did not.

7 Q Are there people at Mass. General who watch for
8 trends like that?

9 A There is a quality assurance program. I am not
10 sure. I do not know if that's one of their
11 charges.

12 Q Well, given your administrative positions and your
13 clinical positions, if there had been some spike
14 in the diagnoses of digoxin toxicity in those
15 years, do you think that's something that would
16 have come to your attention?

17 A I can only say possibly. It's a large
18 organization, and often times there are things I
19 think should have come to my attention earlier
20 than they do, that I eventually find out about,
21 so.

22 There are probably things that I might think
23 should come to my attention that do not.

24 Q Your CV, because of its length, was a bit much to
25 get through all the publications. Have you ever

1 published anything that's primarily about digoxin
2 or cardiac glycosides?

3 A No, I don't believe so.

4 Q I would assume in some of your articles there are
5 references to digoxin because it's a commonly
6 prescribed cardiac drug; is that fair?

7 A That's fair. I can't immediately point to one,
8 but --

9 Q How many times have you been involved in
10 litigation as an expert witness?

11 A Would be approximately -- by an expert witness,
12 just to clarify, you mean giving a deposition or
13 would even just reviewing a case?

14 Q Reviewing cases to start, and I assume some fall
15 off and there is a smaller number that go to
16 report, smaller number that go to deposition, et
17 cetera. So how many cases do you review?

18 A I think perhaps in terms of cases, probably about
19 40 or so over the course of my career.

20 Q How many do you think have gone to report?

21 A Maybe about a dozen.

22 Q What percentage of those have been medical
23 negligence cases as opposed to pharmaceutical
24 products liability cases?

25 A None were pharmaceutical liability, so a hundred

1 percent would be medical negligence.

2 Q Is this the only pharmaceutical products liability
3 consulting arrangement you've had?

4 A Yes.

5 Q I did not bring extra copies of this. I didn't
6 think it was necessary. In 1995, you co-authored
7 a paper in the JACC about a drug called
8 nicardipine.

9 A Nicardipine, yes.

10 Q It's a long time ago. I don't want to get into
11 the details, nor do I even remember what I wanted
12 to ask you about.

13 A You probably just wanted to tell me how impressed
14 you were with it.

15 Q Not with this paper.

16 A Oh.

17 Q Others maybe. I know what it is. Nicardipine is
18 an inotropic drug, correct?

19 A Clarify a little more, meaning does it alter the
20 inotropic state of the heart? Ask me what --
21 rephrase, I'm sorry.

22 Q Well, is it a, is it an inotropic drug or a
23 negative inotropic drug?

24 A I think that one of the conclusions that we came
25 to in that paper was that it had a negatively

1 inotropic effect, yes.

2 Q Okay. Were you exploring it as a possible avenue
3 to be an inotropic effect?

4 A A negative inotropic effect?

5 Q No, a positive one.

6 A No.

7 Q All right. So bottom line, the purpose of this
8 particular research was not to seek an alternative
9 to digoxin for inotropic effect.

10 A That is true.

11 Q All right.

12 A That is correct.

13 Q Okay. Now, in 1996, you co-authored a paper in
14 the New England Journal of Medicine.

15 A Which one is this?

16 Q It's called Apoptosis in Myocytes and End-Stage
17 Heart Failure?

18 A Yes.

19 Q And then in the next year or so, in Journal of
20 Heart and Lung Transplant, you co-authored a paper
21 called Expression of Proinflammatory Cytokines in
22 the Failing Human Heart, and then shortly after
23 that, in Circulation -- I won't ask you about
24 that. Let's just ask you about these two.

25 A Okay.

1 Q You use the term in these two papers, end-stage
2 heart failure; that's in the New England Journal.

3 A Right.

4 Q And in, same in the Journal of Heart and Lung
5 Transplant paper, you talk about end-stage heart
6 failure. How do you define end-stage heart
7 failure?

8 MR. MILLER: Excuse me, Matt, if I could,
9 why don't you let the doctor take a look at those.
10 You're talking about articles that he wrote some
11 13 years ago.

12 Q All I'm asking is how you define end-stage heart
13 failure because I didn't see it in there.

14 A I think for the purposes of these two manuscripts,
15 it was patients who would be anticipated to have a
16 survival without transplantation of less than 12
17 months.

18 Q And what does that, what prognostic features do
19 you use to assess whether a patient is expected to
20 have survival without transplant of less than 12
21 months?

22 A A variety of them. Certainly, their level of
23 symptoms; their frequency of hospitalization;
24 their cardiac function as maybe assessed both
25 invasively and non-invasively; certainly their age

1 factors into that. Their -- we will often
2 quantitatively assess their exercise capacity, if
3 possible; certainly, if they require intravenous
4 agents or mechanical support to keep them alive.
5 Those would be factors that we would consider.

6 Q All right. When you talk about assessing heart
7 function, I assume non-invasively, you're talking
8 about something like an echocardiogram to assess
9 injection fraction, right?

10 A Well, there are a number of parameters you can
11 obtain from an echocardiogram to assess cardiac
12 function, and an echo is one of those techniques,
13 and the injection fraction is one of those
14 parameters.

15 Q And then invasively, are you talking about getting
16 pressures through some sort of catheterization
17 technique?

18 A Again, one of the measurements, one of the
19 assessments.

20 Q And for example, if the judgment is made that a
21 patient needs to be on an IV inotrope like
22 milrinone, is that something that would be
23 significant to you in assessing whether a patient
24 was in end-stage heart failure?

25 A If they required that drug to maintain adequate

1 performance, yes.

2 Q Well, how do you define required?

3 A If their cardiac performance without that agent
4 was insufficient to maintain end organ function.

5 Q Okay. May I have that back.

6 A Sure.

7 Q Do you know whether you have participated in
8 writing any papers that sort of lay out the
9 criteria that you just explained to me in this
10 deposition about how you assess what end-stage
11 heart failure is?

12 A Can I look at my CV?

13 Q Sure.

14 A Yes.

15 Q Are your references numbered in your CV?

16 A Yes.

17 Q Give me a page and reference number, please.

18 A Well, I'm sort of working backwards here, so page
19 46, reference 71, I was a co-author on the paper
20 on looking at physical activity and how it related
21 to life expectancy in patients that were
22 considering VADs. Back a page to 45, reference
23 66, the paper on ventilatory efficiency. The
24 ventilatory efficiency is one of the things we
25 look at as a prognostic marker in patients with

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1 heart failure.

2 Q Are those older papers or some of your more recent
3 ones?

4 A Well, the ventilatory efficiency one was 2008, and
5 reference 71 was 2009.

6 Q Okay. That's all I need then is the more recent
7 stuff.

8 A Okay.

9 Q When you said the word VADs, you're talking about
10 ventricular assist devices, correct?

11 A Right. Sorry, I shouldn't use the lingo.

12 Q That's fine. I'm just trying to help out Lisa.

13 Okay, now, in 2007, you published a paper in
14 Circulation about Sildenafil?

15 A Yes.

16 Q Is that how you pronounce that?

17 A Yes.

18 Q "Sildenafil improves exercise capacity and quality
19 of life in patients with systolic heart failure
20 and secondary pulmonary hypertension."

21 When you do a study like this, and in this
22 one, for example, you assigned a certain number of
23 patients at a certain heart failure level either
24 to the study drugs, Sildenafil, and then a certain
25 number to what's known as placebo, correct?

1 A That is correct.

2 Q And what you're trying to do is blindly assess
3 whether this Sildenafil is better than placebo in
4 a certain treatment regimen, is that right?

5 A Correct.

6 Q When you do a study like this, I assume that you
7 watch for adverse events.

8 A We do.

9 Q Track these patients pretty carefully?

10 A Yes.

11 Q Now, in this particular study, in Table 1 you have
12 something called the Baseline Characteristics of
13 the Study Subjects; do you see that?

14 A Correct.

15 Q And amongst your study subjects in the heart
16 failure pharmacotherapy section, some of them were
17 on digoxin, is that true?

18 A That is correct.

19 Q So when you're doing a study like this, you're not
20 only watching for the potential side effects of
21 Sildenafil, but also of the other drugs that the
22 patient is on?

23 A Yes.

24 Q Did you keep the patients on digoxin during the
25 course of the study?

1 A I'd have to go back and look at the individual
2 patient records and see, you know, who remained on
3 it and who did not.

4 Q Yeah, I didn't see that in the paper. I'm not
5 going to make you go back and look at that, but do
6 you have any memory of whether you would have
7 taken some off and left some on?

8 A We might have. Depends on their clinical course
9 through the study. I think it was a 12-week
10 study?

11 Q Well, forget clinical course for a second, would
12 it have been part of the study design to take some
13 off and leave some on?

14 A I don't believe it was part of the study design.

15 Q But if a patient was doing, for example, got signs
16 or symptoms of digoxin toxicity, you may have
17 taken them off that drug for some period of time.

18 A That is true.

19 Q Do you have any idea, do you track the brand of
20 digoxin that a patient takes when they're in a
21 study like this?

22 A We did not.

23 Q In the testifying that you've done before in med
24 mal cases, has any of that been about digoxin?

25 A I don't immediately recall that digoxin was

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1 involved.

2 Q Do you ever lecture about digoxin?

3 A I do speak about it in my lectures on heart
4 failure that I give to the house staff.

5 Q Do you have a prepared slide deck which includes
6 slides about digoxin in it?

7 A There may be a slide or two, yes.

8 Q You ever participated in any pharmacokinetic
9 studies about digoxin?

10 A No.

11 Q Have you ever published any epidemiologic studies
12 about drug toxicity outbreaks?

13 A No.

14 Q Have you ever been a consultant to pharmaceutical
15 companies on quality control or regulatory issues?

16 A Not quality control. In some of the consulting
17 work that I've done for pharmaceutical companies,
18 I suspect that regulatory issues may have come up.
19 I don't think it was the primary focus of the
20 consultancy.

21 Q Okay. You don't consider yourself to be an expert
22 in FDA regulatory matters, do you?

23 A No.

24 Q I see you've been on the Scientific Advisory Board
25 for a company called iNO Therapeutics; is that

1 true?

2 A I had in the past. I am no longer.

3 Q What did your Scientific Advisory Board work for
4 them involve?

5 A We would review the potential uses and studies of
6 the use of inhaled nitric oxide in a variety of
7 clinical situations.

8 Q Okay. What consulting work have you done for GSK?

9 Before you answer that, there may be ongoing
10 consulting work for which you have a, some sort of
11 secrecy agreement, some confidentiality agreement.

12 A Right.

13 Q All you have to do is tell me that you have
14 ongoing work that's subject to a confidentiality
15 agreement. You don't have to tell me what it is,
16 but if there is stuff in the past you've done that
17 you're allowed to talk about, that's what I want
18 to know about.

19 A I've certainly, I mean, do you want to know about
20 specifics, how specific -- I mean, I've done
21 consulting work for GSK on the development of
22 several agents that they were studying for the
23 treatment of heart failure.

24 Q Okay.

25 A And I've done a small amount of review of events

1 of patients, cardiovascular adverse events of
2 patients that were taking one of the diabetes
3 drugs.

4 Q All right. Did any of your consulting work for
5 GSK involve their digoxin product, Lanoxin?

6 A No.

7 Q You've been on the Scientific Advisory Board for
8 Bayer?

9 A Yes.

10 Q What did you do for them?

11 A That's ongoing. And I imagine that much of that
12 does fall under confidentiality agreements.

13 Q Does any of it involve cardiac glycosides?

14 A No.

15 Q And what do you do on the Scientific Advisory
16 board for Zensun Therapeutics?

17 A They are developing an agent for the treatment of
18 heart failure, and I'm actually not doing that
19 anymore, that anymore, and I consulted on it.

20 Q Right. When you are researching other drugs for
21 heart failure, are some of these ultimately
22 designed to pretty much make digoxin use for heart
23 failure unnecessary?

24 A I don't think they have that specific goal in
25 mind, no. I -- no. I would say not. I think

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1 that we would study adding these agents onto
2 current medical therapy, which often can include
3 digoxin.

4 Q Has your own use of digoxin -- I assume you
5 prescribe digoxin for patients?

6 A I do, yes.

7 Q And has your own prescription rate for digoxin
8 declined over the years from when you first
9 started in this, close to 30 years ago, to now?

10 MR. MILLER: Objection to form. You can
11 answer.

12 A I would say it has.

13 Q Is that because the onset of additional drug
14 therapies that have wider therapeutic windows?

15 A I would say it's been the use and the
16 recommendation by, you know, guidelines such as
17 published by AJACC of agents that have more
18 evidence supporting their beneficial effects in
19 heart failure patients, and has relegated digoxin
20 to a tertiary role, shall I say, for treatment of
21 heart failure.

22 Q And even at normal doses, some of these formal --
23 sorry, even at normal doses, some of these newer
24 drugs are safer than digoxin, right?

25 A Even --

1 Q That didn't make much sense. I'll withdraw it.

2 A Okay.

3 Q I asked you a minute ago about therapeutic window.

4 Do you know what I'm talking about?

5 A Maybe you better elaborate.

6 Q Okay. Toxic therapeutic window, is digoxin
7 considered to have a narrow therapeutic window?

8 A Digoxin is considered to have a narrow window
9 because some patients can have toxicity even at
10 plasma levels that are considered therapeutic, and
11 the difference between plasma levels that can
12 cause toxicity and that a patient may usually have
13 as their therapeutic level is small.

14 Q And furthermore, we'll get into this more later,
15 but patients who are taking appropriately dosed
16 products can get toxicity on digoxin, can't they?

17 A What do you mean by appropriately dosed?

18 Q Well, if they're prescribed a 125 microgram
19 product, and that's what they're taking, they can
20 still get toxicity on normal doses, correct?

21 A I mean, you'd want to look at the individual
22 situation, but there are, you know, situations
23 where toxicity can develop.

24 Q Okay. Would you agree that to some degree there
25 is a catch 22 with digoxin, and that is, that the

1 people who would be most helped by it are
2 sometimes the people who are most vulnerable to
3 complications because of it?

4 MR. MILLER: Objection to form. You can
5 answer.

6 A Certainly there are clinical factors that can make
7 patients have severe heart failure that can render
8 them more susceptible to digoxin toxicity. I
9 don't know that we know exactly who can be most
10 helped by digoxin. We would have some -- we could
11 discuss that if you want, factors that the, you
12 know, are people that are helped as opposed to
13 people that are not helped, but it's hard to know
14 exactly what the determinants of benefit from the
15 digoxin therapy are.

16 Q Let me just ask you about a couple more articles
17 that you wrote. And by the way, if you need to
18 take a break at any point, we can do that.

19 A Okay.

20 Q We tend to take one every hour to hour and a half
21 anyway, but if you need one sooner for any reason,
22 let me know.

23 A Okay.

24 Q In 1994, you co-authored a paper in the Journal of
25 the American College of Cardiology about Exercise

1 Capacity and Systolic and Diastolic Ventricular
2 Function, okay. I'm more than happy to show it to
3 you.

4 A Yes. Yes, I remember that paper. It was actually
5 patients that we studied exercise capacity and
6 systolic and diastolic cardiac function in
7 patients that have recovered from cardiomyopathy.

8 Q It says here, "Dilated cardiomyopathy is a
9 significant cause of cardiovascular morbidity and
10 mortality, particularly among men and women less
11 than 50 years of age."

12 Do you still agree with that?

13 MR. MILLER: Matt, again, I would ask that
14 you give him the document if you're going to ask
15 him about a specific --

16 MR. MORIARTY: If he needs the document, he
17 can ask for it, Pete.

18 MR. MILLER: Well, I'm asking for it for
19 him. Would you please let him review the
20 document.

21 Q Do you want the document?

22 A Let me take a look at the document.

23 Q Sure. You're more than welcome to. You don't
24 have to do things just because Pete wants it. We
25 do it because you and I want it.

1 A Thank you.

2 I would say yes, I still agree with that.

3 Q Okay.

4 A It's not the most precise statement that I've ever
5 written.

6 Q Later in the same page of this, it says, "Although
7 most patients with this disorder die of
8 progressive heart failure or arrhythmia within
9 five years of diagnosis, several recent studies
10 have reported a subgroup of patients who
11 demonstrate spontaneous improvement in ventricular
12 function." Do you still agree with that?

13 A No, I'd have to sort of, the developments in the
14 field, that the first phrase there may not be
15 true. I mean, that was particularly when you deal
16 with the arrhythmia issue, that the development of
17 plantable defibrillators and other therapies have
18 decreased death from both arrhythmia and from
19 progressive heart failure.

20 Q Let me ask you if this statement from later in the
21 article is still true. "Although patients with
22 dilated cardiomyopathy usually have a poor
23 prognosis and an annual mortality rate of 7 to 10
24 percent due to either progressive heart failure or
25 arrhythmia, individual patients may differ with

1 respect to both clinical course and degree of
2 residual ventricular dysfunction."

3 A I would say the first phrase is no longer true.
4 Again, improvements in the field have decreased
5 that mortality rate.

6 Q But do they still usually have a poor prognosis?

7 A It's a very vague statement, and I would say that
8 their prognosis has improved. That was 15 years
9 ago. Pleased to say their prognosis has improved.

10 Q Okay. That's all I wanted to ask you about your
11 own stuff.

12 What has been your involvement in
13 pharmaceutical recalls?

14 A In pharmaceutical recalls.

15 Q Recalls. If any.

16 A None that I can recall.

17 Q All right. Do you know anything at all about the
18 FDA's statutory definition of adulteration of
19 pharmaceutical products?

20 A I do not.

21 Q In the course of -- how did you find out about the
22 Digitek recall?

23 A I believe I may have received a letter from the
24 manufacturer about it a number of years ago, I
25 can't even say precisely when, and then when

1 Carmen Scott discussed it with me.

2 Q Okay. The recall of Digitek was in the end of
3 April 2008 and Actavis did not send out notice to
4 individual cardiologists around the country.
5 Because it's a generic manufacturer, typically it
6 doesn't do that.

7 Having told you that, does that refresh your
8 memory about how you found out about this recall?

9 A I'm just wondering if any of the pharmacies had.

10 Q The pharmacies did send out letters.

11 A Yeah, I think that might be where I got the letter
12 from.

13 Q Once you found out about it, did you do any
14 research about the Digitek recall or Digitek in
15 general?

16 A Not specifically, no.

17 Q What did you do about communicating with patients
18 about their own, if they were on digoxin, whether
19 they were taking that particular brand?

20 A I think that there were -- it was a letter that
21 was sort of, I think might have said specific
22 patients of mine that might have been on it, and I
23 think that there were fairly few, and I looked at
24 their records to see if there was any evidence
25 that they had digoxin toxicity, or as I remember,

1 it could go either way, or inadequate digoxin
2 effect, shall I say. And they didn't.

3 Q Okay.

4 A And then I left it as it was.

5 Q All right. How many -- do you remember how many
6 patients you had on Digitek at the time?

7 A Again, would only be based I think on the letter,
8 a letter or letters I may have gotten from, you
9 know, pharmacies, or you know --

10 Q But that's fine. Do you remember the number?

11 A It was a small number. It was certainly less than
12 ten. It may have been less than five.

13 Q How many patients do you have on digoxin products
14 in general?

15 A I don't know. I do not know. Probably, can I say
16 a few dozen? I'd say probably less than a
17 hundred.

18 Q You can say whatever you want.

19 A I don't know precise number.

20 Q You're under oath. I don't want you to guess --

21 A Right, okay.

22 Q -- is what I'm trying to say.

23 A I do not remember.

24 Q Okay.

25 A I do not know.

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1 Q You see patients in Massachusetts General
2 Hospital, correct?

3 A Correct.

4 Q And then do you have an office where you see
5 patients?

6 A In the hospital, yes.

7 Q Do you have an office outside the hospital?

8 A No.

9 Q So you're not part of a group that may have an
10 office in Newton or Springfield or anything else?

11 A No.

12 Q So after the digoxin, the Digitek recall, did you
13 ever do any research into what the FDA later said
14 about the product?

15 A No.

16 MR. MORIARTY: Why don't we take a
17 five-minute break. We're making pretty good
18 progress and I'm at a natural breaking spot.

19 MR. MILLER: We shall break.

20 (Recess taken.)

21 Q Do you have a copy of your report there?

22 A I do not. I think it was in my file.

23 MS. DOWNIE: Oh, I apologize.

24 Q Have it there?

25 A Yes.

1 Q And that is again Exhibit 42.

2 Obviously, whether a doctor decides to use a
3 digoxin product in a heart failure or a-fib
4 setting is the choice of the physician, correct?

5 A Yes.

6 Q And then the physician is the one who chooses the
7 dose, correct?

8 A Yes.

9 Q Are there patients for whom you have what I would
10 call odd doses where they either take half of a
11 standardized dose, or you know, like a .375 dose
12 per day or something like that?

13 A The dose varies a great deal from patient to
14 patient, yes.

15 Q What is the maximum dose that you currently
16 prescribe any of your patients for digoxin?

17 A I think the maximum dose that I currently
18 prescribe is approximately 250 micrograms a day.

19 Q In the past, have you had patients who were on 375
20 mic's a day?

21 A I don't think I've ever prescribed quite that
22 high, no.

23 Q So I assume you haven't prescribed 500 mic's a
24 day.

25 A Not on a chronic basis, no.

1 Q Do you know whether any of your atrial
2 fibrillation colleagues here at Mass. General
3 prescribe doses as high as 500 mic's a day?

4 A I don't know.

5 Q So on the first page of your digoxin toxicity
6 statement, at the end of the second paragraph,
7 talks about the frequency of digoxin toxicity
8 which is related to the occurrence of toxic
9 effects at plasma levels that are in the upper
10 range of what is considered therapeutic; do you
11 see that?

12 A Yes.

13 Q I assume what you're referring to is that some
14 patients who may have a serum digoxin
15 concentration of 1.8, for example, might
16 demonstrate signs or symptoms of toxicity, is that
17 correct?

18 A I think that that is, that statement is correct;
19 they do do that, yes.

20 Q And those patients could be taking appropriately
21 dosed pharmaceutical products, correct?

22 A I don't know if I would say it's appropriately
23 dosed if -- it's hard to, I don't know what you
24 mean by the word appropriate.

25 Q Well, again, have you ever had a circumstance

1 where you suspected that patients of yours were
2 taking digoxin products that were, had active
3 pharmaceutical ingredient levels higher than their
4 labeled amounts?

5 A There certainly have been situations where I
6 considered that possibility, yes, because I could
7 not understand why they had clinical toxicity as
8 well as, yes, sometimes substantiated by levels
9 higher than I would have anticipated and had no
10 other explanation.

11 Q Did you investigate it?

12 A I didn't because I think one of the things that we
13 were taught was that in olden times, shall we say,
14 perhaps, you know, maybe when, you know, prior to
15 when I completed my training in 1989, that there
16 could be a lot of variability in digoxin
17 preparations in terms of their, how much of the
18 active ingredient they had.

19 Q Do you know whether that situation has pretty much
20 been eradicated by the FDA's requirements that
21 companies file bioequivalency studies?

22 A My understanding was that it has been
23 significantly reduced, yes.

24 Q But certainly in your own practice, there are
25 times when you've had patients in whom you're

1 prescribing a particular dose, and their response
2 is not what you would expect, correct?

3 A There have been occasions.

4 Q To digoxin specifically.

5 A There have been occasions when the response to
6 digoxin, shall I say either way, has been greater
7 or less than anticipated.

8 Q At Mass. General, I assume you have serum digoxin
9 concentration studies available?

10 A We can send patients for laboratory tests, yes.

11 Q When the lab slip comes back, what is the range of
12 therapeutic on your Mass. General lab slips?

13 A I don't think they designate it as therapeutic. I
14 think they will designate toxic. I'm actually, I
15 don't know if I know for sure what they are
16 currently saying.

17 Q Well, most of the lab slips, emphasize most, that
18 I have seen as I've gone through medical records
19 in this litigation, is .8 nanograms per milliliter
20 to 2.0 nanograms per milliliter. Do you know if
21 that's what the range is for normal so-to-speak on
22 the Mass. General lab slips?

23 A Again, I think they just designate a toxic greater
24 than as a level. I don't think they designate a
25 range, as you say, of normal.

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1 Q And what about, what would the toxic greater than
2 level be?

3 A I'm not sure whether it's 1.7 or 2.0. I don't
4 recall. I'd have to look. It may be another
5 number. I would just have to look.

6 Q Let's go to page 3, please. In the section
7 called: Clinical Use of Digoxin, Heart Failure.

8 A Yes.

9 Q In the second paragraph, you refer to a landmark
10 1982 study at Mass. General.

11 A Yes.

12 Q Were you involved in that study?

13 A No.

14 Q This would have been just after your completion of
15 medical school, correct?

16 A No. I graduated in '83.

17 Q Oh, okay. So you would have still been in medical
18 school.

19 A Correct.

20 Q Go to page 4, please. The, in the center of the
21 page of Current Guideline Recommendations for the
22 Use of Digoxin to Treat Heart Failure Patients, do
23 you see that?

24 A Yes.

25 Q And you refer to item reference 5; correct?

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1 A Yes.

2 Q Is that meant to refer to the fifth reference on
3 page 12 of your report?

4 A Yes.

5 Q So you're talking here about the 2009 guidelines,
6 is that right?

7 A Yes. I believe so. I have a copy of them, the
8 update of the 2005 guidelines.

9 Q So let's skip quickly to page 8, and then we'll
10 come back to this.

11 A Okay.

12 Q Under, Plasma digoxin levels?

13 A Um hmm.

14 Q Third paragraph. Says, "A plasma digoxin level of
15 greater than 2.0 ng/ml is considered toxic, though
16 as noted above, the presence of the ischemic heart
17 disease, hypokalemia, or other metabolic
18 abnormalities cited above can lead to toxic
19 effects at lower levels."

20 First of all, did I read that correctly?

21 A Yes.

22 Q And when you say digoxin level of greater than 2
23 is considered toxic, is that your experience, or
24 is there a particular piece of medical literature?

25 A I think it's in my experience in and of itself

1 that that's toxic, yes.

2 Q So let's go down to the bottom, go back to page 4,
3 please, go to the bottom, talking about Digoxin
4 Toxicity and some Epidemiology, is that right?

5 A Yes.

6 Q "Digoxin toxicity remains one of the most
7 prevalent adverse drug reactions seen in clinical
8 practice."

9 Did I read that clause correctly?

10 A Correct.

11 Q And why is that?

12 A I think that that is because its toxic effects can
13 be -- there are a number of reasons. Among them
14 are the fact that its toxic effects can be seen at
15 levels that are relatively close to those
16 considered therapeutic. I think I discuss some of
17 this in the Factors leading to or contributing to
18 digoxin toxicity.

19 Q We'll get there.

20 A So that's sort of what I'm referring to.

21 Q Okay.

22 A That there can be, you know. So one of them is
23 the narrow difference. Another is changes in
24 absorption and excretion. Another is that, you
25 know, changes in its bioavailability or amount of

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1 drug in the formulation. Pretty much what I go
2 into in that paragraph.

3 Q Okay. And this statement that you make at the
4 bottom of page 4 isn't product specific in your
5 report, is it?

6 A No, it's not.

7 Q I mean, this is true for all digoxin products, is
8 that right?

9 A Correct.

10 Q So let's go to page 5. First full paragraph, you
11 start out by talking about the DIG trial, correct?

12 A Right.

13 Q And you say, "12 percent of the patients in the
14 treatment arm were suspected of having digoxin
15 toxicity," is that correct?

16 A Yes. That's what I said.

17 Q And nobody certainly in the DIG trial ever made a
18 conclusion that the digoxin products being given
19 to those patients were defective in their dosage,
20 correct?

21 A I'd have to review. I don't remember all the
22 wording there.

23 Q Review away.

24 A Okay.

25 Q I can assure you there's nothing about that in the

1 paper that is in your folder, but you can check.

2 Are you looking at the New England Journal
3 of Medicine article from February of 1997?

4 A Yes.

5 Q By the way, this is reference 7 in your report.

6 A Okay. So ask your question again. I'm sorry.

7 Q There was nothing in the DIG trial report,
8 Exhibit, or Tab 7 to your reference section about
9 defective digoxin products causing toxicity,
10 correct?

11 A Correct. They only used one product as their
12 study.

13 Q While we're on this DIG trial, let me just ask you
14 what I need to ask you about it. Go to page 527.
15 In the Results section, see Mortality?

16 A Um hmm.

17 Q There were 1181 deaths in the digoxin group, 34.8
18 percent of the study; correct?

19 A Um hmm.

20 Q That's a yes?

21 A Yes.

22 Q That's just a reflection of the fact that these
23 are sick people and they die of their disease
24 despite appropriate therapy, correct?

25 A I think in the next paragraph they're actually

1 even more specific and they tell you what the
2 number of deaths were from cardiovascular causes,
3 so 1181 total deaths, and then the next paragraph,
4 1016 deaths from cardiovascular causes.

5 Q In other words, their underlying disease.

6 A Yes. Usually, yes.

7 Q Now --

8 A I mean, there could have been other cardiovascular
9 deaths in there as well that had developed during
10 the course of the study.

11 Q Now, in your report at page 5, you refer to this
12 12 percent of the patients in the treatment arm.
13 That's the patients who were taking digoxin in the
14 DIG trial; correct?

15 A Correct.

16 Q The other arm is the control arm or the placebo
17 arm, right?

18 A Yes, so I think that what I said -- where are we
19 now?

20 Q Page 5, first full paragraph.

21 A Were suspected of having digoxin toxicity, right.
22 That's the number of patients that were suspected
23 of having digoxin toxicity.

24 Q In the treatment arm.

25 A In the treatment arm, correct.

1 Q And then there's another arm, the placebo arm.

2 A Right.

3 Q Actually, in the DIG trial, there was a
4 substantial percent of the placebo patients not
5 taking digoxin at all who were suspected of having
6 digoxin toxicity, is that right?

7 A As I recall, yes. Let me look that up. 7.9
8 percent.

9 Q And that's because some of the signs and symptoms
10 of digoxin toxicity are vague and can look like
11 all kinds of other diseases, is that right?

12 MR. MILLER: Object to form.

13 A Yeah, I wouldn't use the word vague. I would say
14 that some of the manifestations of digoxin
15 toxicity may not be -- some of the manifestations,
16 or that we consider to be potentially related to
17 digoxin toxicity, can occur in the absence of
18 digoxin.

19 Q In other words, they're nonspecific.

20 A Some of them are. Many of them are.

21 Q And at page 530, look at the serum digoxin level
22 section; do you see that?

23 A Yes.

24 Q Certainly, they, in the DIG study, obtained all
25 the samples, the SDC samples more than 6 hours

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1 after the last dose, is that correct?

2 A Correct.

3 Q Is that the right way to do it?

4 A Well, they were looking for steady state levels,
5 and that's the right way to look for what
6 somebody's steady state level is.

7 Q Down further it actually talks about what some of
8 the doses were in the DIG study. I believe these
9 were customized, but do you see that some of the
10 patients were getting 375 micrograms per day and
11 some were getting 500 mic's per day?

12 A That is what it says, yes.

13 Q Does it say anywhere in the DIG trial that all the
14 patients who got 375 or 500 micrograms per day
15 became digoxin toxic or were suspicious of being
16 digoxin toxic?

17 A Does not say anything about all of those patients.
18 Can I reflect back on an earlier answer to a
19 question?

20 Q Sure.

21 A Well, it does say, and I would actually, should
22 have mentioned this earlier, you had asked about
23 the appearance or suspicion of digoxin toxicity in
24 the placebo arm, but a significant number of
25 patients in the placebo arm were taking digoxin.

1 It does say that.

2 Q Where does it say that?

3 A 530, second column, it says, "Open-label digoxin
4 was used sometime during the trial by 14.2 percent
5 of patients in the digoxin arm as compared with 22
6 percent of those in the placebo group." So 22
7 percent of the patients in the placebo group were
8 at some time taking digoxin.

9 Q Okay. Obviously, you know a lot more about
10 control trials than I do, but why would you have
11 patients in the placebo arm at some point taking
12 digoxin?

13 A From the investigator's point of view, it's a big
14 problem because you obviously want your groups to
15 be as pure as possible. From the point of view of
16 the physician taking care of these patients, if
17 they thought they needed digoxin, they were going
18 to prescribe it for them.

19 Q Okay.

20 A It's a big problem in clinical research.

21 Q It probably wasn't part of the study design to
22 have placebo patients taking digoxin. It's one of
23 those things that you mentioned earlier that could
24 just come up in clinical course, is that right?

25 A It happens in clinical research. You know, if

1 physicians feel a patient needs medication,
2 they're going to give it to them. They're going
3 to feel ethically bound to do it.

4 I guess in the terms of study design, one
5 could mandate that patients, should the
6 investigator feel they need to go on digoxin, one
7 could mandate that the patient drop out of the
8 study at that time, and in terms of study design,
9 sounds like they did not do that.

10 Q And finally on page 532.

11 A Yes.

12 Q Second full paragraph, last sentence. It says,
13 "The vast majority of the study patients had serum
14 digoxin levels in the therapeutic range at the one
15 month visit and only 2 percent had levels
16 exceeding 2.0 nanograms per milliliter." Did I
17 read that correctly?

18 A You did.

19 Q Let's get back to your report at page 5, last
20 sentence in that paragraph that we were just
21 talking about. It says, "Older patients, and
22 those with the most severe heart failure, are at
23 greatest risk for an adverse outcome during an
24 episode of digoxin toxicity."

25 First of all, older patients are at the, are

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1 among a group of patients at higher risk for
2 digoxin toxicity; isn't that true?

3 A I don't know. I mean, I think they, I'd have to
4 think about that. You know, that's not what I
5 meant to say here. I don't think I did say that.

6 Q No. That's not what you said. I asked you a
7 different question.

8 All right, we'll get into that later.

9 A Yeah, I'd have to --

10 Q We'll get into that later. Go to the next
11 section, Factors leading to or contributing to
12 digoxin toxicity.

13 A Yes.

14 Q I think in the first sentence there is a typo.
15 Should that say, A number of factors that have
16 even a modest effect on digoxin levels?

17 A Yes, you're right. Thank you.

18 Q Can lead to digoxin toxicity.

19 A Yes.

20 Q All right. I want to hand you a paper written by
21 Bigger in a Journal of Clinical Pharmacology back
22 in 1985. And the only thing I want to ask you
23 about is whether Table 1 on the second page of
24 that article is a reasonably reliable summary of
25 what you're talking about in the first sentence of

1 this section of page 5 of your report.

2 A The first sentence.

3 Q Yes. You're saying, "A number of factors that
4 have even a modest effect on digoxin levels can
5 lead to toxicity," and I'm asking whether Table 1
6 is a reasonable summary of what some of those
7 factors are.

8 A I guess it does state some of the factors that I
9 was referring to. I am confused by one thing that
10 they say, or he says, I guess, there's only one
11 author, right, where it says, "reduce volume and
12 distribution," and then he says, "ventricular
13 failure shock." I'm not sure how that affects the
14 volume of distribution of the drug. I just don't
15 understand that.

16 Q Okay.

17 A And then I would need to know a little more, maybe
18 I could read through this, about how excess
19 sympathetic activity can cause digoxin toxicity.

20 Q Other than those two, it's a fair summary?

21 A Other than those two, it says some of the factors.

22 Q All right. Now, are there factors beyond what's
23 in Bigger's Table 1 that bear on your statement on
24 page 5 of your report?

25 A Can I see the Table 1 again.

1 Well, I talked about the possibility of
2 increased absorption of the medication. I'm not
3 sure if that's really included here. And I would
4 also relate, and factors that might cause
5 conduction system disease, and he doesn't really
6 directly address that.

7 Q Such as?

8 A Either intrinsic or other agents that alter
9 cardiac electrical conduction, I would say.

10 Q Okay.

11 A There could be agents. There could be intrinsic
12 disease of the conduction system.

13 Q Can increase the risk of toxicity?

14 A I would think so, yes.

15 Q Later in that same paragraph in your report, you
16 say, "Small changes in the amount of drug in the
17 formulation, or its bioavailability, can lead to
18 clinically significant changes in plasma levels;"
19 do you see that?

20 A Yes.

21 Q So in other words, that's a possibility?

22 A Yes.

23 Q And you know the difference between possibility
24 and probability? You've dealt with that in
25 medical negligence cases?

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1 A Yes, sure.

2 Q All right. And the next full paragraph, you start
3 talking about drug interactions; do you see that?

4 A Just to elaborate on that, a possibility can
5 become a probability when other possibilities are
6 less likely. At least that's my thought.

7 Q Okay. So the next paragraph starts talking about
8 drug interactions; do you see that?

9 A Yes.

10 Q Do you keep Braunwald's cardiology text in your
11 home or office medical library?

12 A I do.

13 Q Is it a good, reliable text in cardiology?

14 A Much of it is. Some of it, less so.

15 Q Well, then let's talk about one particular part
16 and see if it is or not.

17 A Okay.

18 Q This is a table, Table 23.4 from Braunwald's text.

19 A Um hmm.

20 Q I'm just wondering whether you consider that to be
21 a reasonable, reliable, partial list of drugs that
22 have the potential to somehow interfere with
23 digoxin.

24 A I don't know. Meaning I'd have to look at the
25 specific drug and the literature that supported or

1 not, you know, the basis for this statement. I
2 mean, so it's hard to judge.

3 Q Is there anything on the list that jumps out at
4 you that you disagree with?

5 A I'd need to -- I have not heard, for example, I
6 don't recall tetracycline altering digoxin or
7 interacting with digoxin as they say. So that's
8 one that jumps out, and I'd need to review the
9 others, some of the others.

10 Q All right. If you were going to check on your own
11 for whether there was going to be an interaction
12 between digoxin and some other drug, what sources
13 would you typically look to?

14 A As we said earlier, look at the prescribing
15 information for digoxin, prescribing information
16 for the other drug.

17 Q Okay. You're right. We talked about that.

18 But I don't remember if I asked, would you
19 ever use the PDR?

20 A Probably not. You know, actually, I don't use it
21 very much anymore. There are these on line
22 compendias of drugs. There's the FDA site, and
23 there's the availability so readily to go to the
24 direct literature.

25 Q Okay. Go to page 6 of your report, please.

1 Symptoms and signs of digoxin toxicity.

2 You're talking about these as being
3 nonspecific, and then you say they include
4 fatigue, blurred vision, and you go on with a list
5 of things I don't need to read; do you see that?

6 A Yes.

7 Q Now, in most cases when patients become digoxin
8 toxic, do they start with these nonspecific
9 symptoms?

10 A We'd have to look at individual cases. I mean, in
11 many cases they do. And in many cases, they start
12 with the, with an abnormal rhythm.

13 Q All right. Well, let me jump to an end point.
14 How many times in your career have you had a
15 patient die of a sudden cardiac death to which you
16 attributed the cause to be digoxin toxicity?

17 A Probably -- I don't know exactly. It certainly
18 has happened.

19 Q Right, I don't mean to cut you off, but if you
20 look at your entire career, the number of times
21 you've diagnosed digoxin toxicity, the number of
22 times a patient has died a sudden cardiac death
23 without having experienced some of these
24 nonspecific symptoms first would be a substantial
25 minority, wouldn't it?

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1 A Relative to minority -- what's the comparison?

2 Q Okay. Let's say your diagnosis of digoxin
3 toxicity is a universe of a hundred percent.

4 A Okay.

5 Q The number of patients who have died a sudden
6 cardiac death without these nonspecific symptoms
7 in some way having occurred first, would be a
8 substantially small percent of your patient
9 population?

10 A I'd say it's been a minority.

11 Q Okay. Well, when you say minority, it's well less
12 than 50 percent, isn't it?

13 A Right, but it's not, it's I think more than one or
14 two percent.

15 Q Okay. So put another way, typically, patients
16 will have some of these nonspecific symptoms
17 before they progress to serious arrhythmias or
18 death.

19 A Well, certainly death. I mean, you asked about
20 death. You asked about sudden death actually, to
21 be specific.

22 Q Right.

23 A I would certainly say that there have been a
24 number of times when patients have presented with
25 arrhythmias without preceding symptoms.

1 Q Okay. Patients who are taking digoxin, even when
2 they're not toxic, can have arrhythmias, can't
3 they?

4 A That is true.

5 Q And that's essentially one of the things you're
6 saying in the first sentence of your next section,
7 about electrocardiographic manifestations of
8 digoxin toxicity.

9 The electrocardiogram is altered by even
10 therapeutic levels of digoxin, correct?

11 A I'm sorry, I don't -- I'm saying that the
12 electrocardiogram is altered by therapeutic levels
13 of digoxin.

14 Q Okay.

15 A That's just what I'm saying.

16 Q All right.

17 A I'm not saying anything more about -- that's not
18 meant to refer to arrhythmias.

19 Q Okay. Well, certainly one of the purposes of the
20 drug is in some ways to alter the
21 electrocardiogram in an a-fib patient, right?

22 A We don't know -- no, I don't agree with that. We
23 don't give digoxin to alter electrocardiograms.

24 Q Well, obviously not to alter the
25 electrocardiogram, but to reduce the atrial

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1 fibrillation.

2 A I mean, we, in atrial fibrillation we give digoxin
3 to slow the ventricular rate.

4 Q Does that, when measured, change the
5 electrocardiogram pattern?

6 A It changes the heart rate which is indicated by
7 electrocardiogram.

8 Q All right. Let's go to page 7. Lab Findings.

9 A Yes.

10 Q Can patients who have elevated potassium levels
11 who are not on digoxin have arrhythmias on sudden
12 cardiac deaths?

13 A Yes.

14 Q Is that true of patients who have subnormal levels
15 of potassium?

16 A They can also have arrhythmias, yes.

17 Q Page 8. Second paragraph of your Plasma digoxin
18 level section.

19 A Yes.

20 Q You see it has, you're talking about endogenous
21 digoxin-like substances, correct?

22 A Yes.

23 Q Sometimes abbreviated in the literature as DLIS,
24 is that right?

25 A I can vaguely remember that.

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1 Q Are there patients who are not taking digoxin but
2 in whom if you drew a serum digoxin concentration
3 level, would have levels indicated by the test?

4 A I think that that's been reported to occur. I
5 think it is less common with some of the more
6 modern assays that are used, and you need to
7 really look at the specific assay and look into
8 the details of it to see if, you know, whether the
9 manufacturer has excluded that. They often test
10 for it.

11 Q My understanding of the way these assays work is
12 that they actually, serum digoxin concentration
13 does not actually directly measure the level of
14 digoxin in the sample. It does it by some derived
15 method. Do you know anything about that?

16 A No. I thought that they were as specific as they
17 could be for directly measuring. Maybe -- I don't
18 see where you're going.

19 Q I may be mistaken too.

20 A Yeah. And I know the assays differ.

21 Q Let's go to page 9, your Summary.

22 A Yes.

23 Q You're talking about, "Among its causes are the
24 acute ingestion of a supratherapeutic amount of
25 the drug."

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1 Now, patients, you're well-aware
2 historically, there are patients who have
3 accidentally taken too much digoxin; is that
4 right?

5 A Yes. I am aware of that.

6 Q And then there are patients who accidentally take
7 too much digoxin for whatever reason; correct?

8 Sorry, let me start over. I may have
9 misspoke. There are patients who intentionally
10 take too much digoxin, typically in suicide
11 attempts, correct?

12 A Yes, that's my understanding.

13 Q Then there are patients who accidentally take too
14 much digoxin, correct?

15 A Yes. I've heard that as well.

16 Q And therefore, essentially two ways you can
17 accidentally take too much digoxin. You can just
18 take too many tablets at a time, is that right?

19 A That would be one way.

20 Q Or you could unknowingly take a tablet of digoxin
21 and have an inappropriate level of the active
22 pharmaceutical, correct?

23 A That would be correct, yes.

24 Q And if you go to these Poison Center statistics
25 that are the references 8 and 9 in your report,

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1 they talk a lot about these sort of things, don't
2 they?

3 A I remember they do.

4 Q They report the instances of intentional overdose
5 of various substances, is that right?

6 A Right.

7 Q And they report the accidental ingestion of
8 various substances, is that correct?

9 A Right. They report based on what is reported to
10 them, which you know, is probably a minority of
11 what happens out there.

12 Q Are you familiar with the FDA's adverse event
13 recording data base?

14 A I know of it, yes.

15 Q And that's a voluntary reporting system, is it
16 not?

17 A Correct.

18 Q Is this Poison Center compendium of statistics
19 also a voluntary reporting system?

20 A I believe it is, yes.

21 Q And the -- your references 8 and 9 in these Poison
22 Center statistics have warnings and disclaimers
23 about the usability of this data to draw
24 conclusions, right?

25 A That is correct, yes.

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1 Q Now, when you dig into these, they do report and
2 break down the substances that people supposedly
3 are poisoned by into various categories, right?

4 A I'd have to look at it again.

5 Q Well, you've got illegal drugs, and you've got
6 pharmaceutical products, broadly speaking, in
7 these compendium, correct?

8 A I don't know. I haven't looked at it in a little
9 while. I actually didn't bring a copy, so --

10 Q I believe they're in your manila folder.

11 A The, no, I think I said at the beginning I didn't
12 bring these.

13 MR. MORIARTY: I thought I saw them in the
14 manila folder.

15 MR. MILLER: I don't think they are, Matt.

16 Q Just check because I thought I saw them.

17 A Sure.

18 Q If you don't have them, that's fine. I'm happy to
19 hand them over to you.

20 A They're pretty thick, so this is the guidelines.

21 Q That's fine. Do you mind if I come over there?

22 A No.

23 Q I'm looking at reference 8 which is the 2006, and
24 so in Table 18 at page 832, you've got these
25 broken down categories associated with the largest

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1 number of fatalities, and they've got sedatives,
2 opioids, cardiovascular drugs, et cetera, correct?

3 A Yes.

4 Q And then in Table 19, they've got comparative
5 fatality numbers for all the years they've been
6 doing this, and '05 and '06 aren't substantially
7 different, correct?

8 A They are similar, yes.

9 Q Actually, there was a decrease in fatalities
10 reported to this data bank; right?

11 A Yes. A slight decrease, yes.

12 Q And then back here at page 851, we're in the
13 cardiovascular drug section, correct?

14 A Yes.

15 Q And then these are just essentially what you as a
16 physician call case reports.

17 A Yes, looks like they were prepared by line
18 summaries of individual cases.

19 Q A number of these are cardiac glycosides, is that,
20 are they not?

21 A Yes.

22 Q And it doesn't say anywhere on here what product
23 is involved, correct?

24 A That is correct.

25 Q Brand name, I mean.

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1 A They say it's digoxin but they don't give a brand
2 name, correct.

3 Q All right. And then Tab, reference 9, same thing,
4 you've got your warnings about the use of the
5 data. You've got disclaimers about the use of the
6 data. You see where I'm pointing to those?

7 A I do. Let's see what they say there. Only
8 provide when they're actually reported. They
9 don't verify the reports or the accuracy, and they
10 should not be construed to represent the complete
11 incidence of national exposures to any substance.

12 Q Okay. And again, Limitations and plans, page 931,
13 their spontaneous self-reported reflect the
14 limitation of this type of reporting system,
15 right?

16 A Yes.

17 Q But they still have statistics at page 938, for
18 example, about inadvertently taking medications,
19 right?

20 A They do give them, yes. Yes, they do.

21 Q Up top in the narrative section, they talk about
22 255,732 therapeutic error instances, the most
23 common being inadvertent double dosing, right?

24 A Yes.

25 Q And in your experience, this is a substantial

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1 problem among patients, particularly the elderly,
2 isn't it?

3 A It occurs. I don't know, I wouldn't call it a
4 substantial problem in my experience.

5 Q Are you familiar with statistics nationally on
6 this?

7 A No, I am not.

8 Q And then again, here at page 945 when they're
9 reporting the mortality statistics, they haven't
10 changed at all or --

11 A Slight increase.

12 Q They certainly haven't changed substantially from
13 2006, right?

14 A To 2007.

15 Q Okay.

16 THE WITNESS: Can I take a quick break?

17 MR. MORIARTY: Absolutely.

18 (Recess taken.)

19 Q Dr. Semigran, is it fair to say that almost all
20 prescription medications have risks?

21 A I think many do, yes.

22 Q And some of them have the risk up to and including
23 death, is that correct?

24 A I think that that's accurate, yes.

25 Q And when you as a physician prescribe medications,

1 it's your job to take into account the risks and
2 make a risk benefit analysis for your individual
3 patient, correct?

4 A Correct.

5 Q Is the same, do you go through the same process
6 when you prescribe digoxin for patients?

7 A Yes.

8 Q I think --

9 A Just to elaborate a little bit, I mean, I think
10 when we even decide on the dose of the digoxin, we
11 make a similar kind of analysis because of the
12 risks of toxicity.

13 Q Right. I think I asked you this before, but you
14 haven't seen any plaintiffs' expert's reports in
15 this case?

16 A Yes, you asked me that and I said no.

17 Q And so you don't really know whether they're using
18 evidence based medicine and reliable methods to
19 come to any of the conclusions that they make in
20 those individual cases?

21 A I don't know anything about the reports.

22 Q And you know what evidence based medicine is,
23 don't you?

24 A It's a term that's, you know, used a lot. I mean,
25 I generally consider it meaning making decisions

1 based on the results of data obtained on certain
2 situations.

3 Q And I believe the American College of Cardiology
4 talks in its publications about sort of believing
5 that evidence based medicine is the appropriate
6 path to follow, correct?

7 A I can't specifically cite an ACC publication,
8 but --

9 Q Do you know if they do, or don't you know?

10 A Many academic and regulatory agencies talk about
11 it, yes.

12 Q Do you know that the ACC has a code of ethics with
13 a, How you should be an expert witness section?

14 A Yes, they do.

15 Q And you would hope that your cardiology colleagues
16 would follow that?

17 A I would hope so, yes.

18 Q You know what Glomerular Filtration Rate is?

19 A Yes.

20 Q GFR, to make my life easier?

21 A Sure.

22 Q Does it slow down with advancing age?

23 A It does decrease with age, yes.

24 Q Does renal function diminish with advancing age?

25 A If the measurement of renal function you're using

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1 is GFR, yes, it does.

2 Q Does muscle mass typically decrease with advancing
3 age?

4 A It can, though that's, that can vary from person
5 to person.

6 Q Do you generally agree that the serum creatinine
7 underestimates the decrease in GFR with age?

8 A I think I need to know about the specific
9 situation there.

10 Q Let me put it another way, do you agree that a
11 serum creatinine in the upper normal range may
12 already reflect impaired renal function in an
13 elderly patient?

14 A It's possible, yes.

15 Q Well, I'm looking at Reference 1 of yours, which
16 is co-authored by Kirkwood Adams is the easiest
17 name to pronounce.

18 A Mihai Gheorghide, yes, and Kirkwood Adams.

19 Q And at page 2962, it says under the category of
20 Elderly, "Because the elderly have a lower lean
21 body mass and decreased renal function, digoxin
22 should be used with caution;" do you agree with
23 that?

24 A I think that's a reasonable statement.

25 Q I want to show you what has been marked as

1 Plaintiff's, or I'm sorry, Defendant's Exhibit 8.

2 I apologize in advance for the size of the
3 reproduction because it puts a real strain on your
4 eyes.

5 A Um hmm.

6 Q But that's the Detailed Patient Labeling for
7 Digitek. Do you recall ever reading the Detailed
8 Patient Labeling for Digitek?

9 A I don't recall, no.

10 Q Just want to go over a couple of things that are
11 in there to see whether you agree or disagree with
12 them. First of all, do you know whether or not
13 this is an FDA approved labeling document?

14 A I do not know. If it was found through the FDA
15 website, for example, it would be.

16 Q Okay. Second column, last paragraph, says, "The
17 clearance of digoxin can be primarily correlated
18 with renal function as indicated by creatinine
19 clearance. The Cockcroft and Gault formula for
20 estimation of creatinine clearance includes age,
21 body weight and gender." Do you agree with that?

22 A With both sentences?

23 Q Yes.

24 A I think I do, yes.

25 Q Right. Let's go to the fourth column. Almost to

1 the bottom, it says: Precautions.

2 A Yes.

3 Q "Use in patients with impaired renal function:
4 Digoxin is primarily excreted by the kidneys;
5 therefore, patients with impaired renal function
6 require smaller than usual maintenance doses of
7 digoxin." Do you agree with that?

8 A I think it's a very general statement, and I think
9 you have to be patient specific when you determine
10 the dose of digoxin and consider the renal
11 function in that, when you prescribe a given dose
12 of digoxin.

13 Q Well, let's go to the last column on that first
14 page.

15 A Yes.

16 Q The last paragraph in the Drugs Interactions
17 section. So it's three-quarters of the way down.
18 "Due to the considerable variability of these
19 interactions, the dosage of digoxin should be
20 individualized when patients receive these
21 medications concurrently." They're referring to
22 medications that are discussed above. Do you
23 agree with that statement?

24 A I agree with that, yes.

25 Q And then it goes on to say, "Furthermore, caution

1 should be exercised when combining digoxin with
2 any drug that may cause a significant
3 deterioration in renal function since a decline in
4 glomerular filtration or tubal secretion may
5 impair the excretion of digoxin;" do you agree
6 with that?

7 A I would agree, yes, caution should be exercised.

8 Q Then on the next page.

9 A I just add that that involves, you know,
10 consideration of the individual circumstances of a
11 given patient.

12 Q Sure. Third column, Dosage and Administration.
13 "In selecting a dose of digoxin, the following
14 factors must be considered," and then there are
15 items one through four; do you see that?

16 A I would agree with that.

17 Q All right.

18 A I think there are other factors as well, but I
19 think that those are among the factors.

20 Q What other factors would you include?

21 A I think the indication for digoxin would be
22 another factor: Is this for heart failure; is
23 this for weight control and atrial fibrillation.
24 Factors that may alter the absorption of the
25 digoxin is another issue.

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1 Q Okay.

2 A There may be a couple of others. Those are the
3 two that come to mind.

4 Q Then there is a, the next paragraph says, Serum
5 Digoxin Concentration; do you see that?

6 A Yes.

7 Q Says, "In general, the dose of digoxin should" --
8 I'm sorry, "The dose of digoxin used should be
9 determined on a clinical grounds." Do you agree
10 with that?

11 A Yes.

12 Q Then they talk about the use of serum digoxin
13 measurements.

14 A Yes.

15 Q I'm looking for the statement I need. It says,
16 "Since one-third of patients with clinical
17 toxicity have concentrations less than 2 nanograms
18 per milliliter, values below 2 nanograms per
19 milliliter do not rule out the possibility that a
20 certain sign or symptom is related to digoxin
21 therapy;" do you agree with that?

22 A I'm reading through the -- because the sentence
23 starts out, "However," so it's somehow referring
24 to the previous sentence as well. So I'm trying
25 to look at that.

1 Says, "About two-thirds of adult patients
2 with clinical toxicity have serum DIG
3 concentrations greater than 2 nanograms. However,
4 since one-third with clinical toxicity have
5 concentrations less than 2 nanograms per ml,
6 values below 2 nanograms per ml do not rule out
7 the possibility that a certain sign or symptom is
8 related to DIG therapy." I would probably add, or
9 toxicity to that in order to agree with it.

10 Q Do you have any idea how many people in the United
11 States were prescribed digoxin between 2006 and
12 2008?

13 A No.

14 Q Do you know how many prescriptions were written
15 for digoxin between 2006 and 2008?

16 A No.

17 Q Do you know what the number is per annum?

18 A No.

19 Q Do you know anything about the breakdown of how
20 many might have been taking Digitek as opposed to
21 Lanoxin?

22 A No.

23 Q Let's go back to Reference 1, this article by
24 Adams and that gentleman whose name you're good at
25 pronouncing.

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1 A Gheorghide, yes.

2 Q Do you know him, by the way?

3 A Yes.

4 Q No wonder you could do it. Page 2961, please,
5 third column, second full sentence. Says, The
6 intoxication is not only dose dependent, but is
7 also related to concurrent medications or
8 conditions." Do you agree with that?

9 A No, I would alter that sentence that it "can" be
10 related, but to say that is, is, it means that --
11 no, I don't agree with that sentence.

12 Q Well, in any case where you suspect digoxin
13 toxicity, you do look into concurrent medications
14 and conditions; don't you?

15 A Yes.

16 Q That's part of your differential diagnosis in
17 ruling out other causes of digoxin toxicity than
18 dose?

19 A I think in trying to determine, yes, the etiology
20 of the digoxin toxicity.

21 Q And would you agree that digoxin toxicity is a
22 known and accepted risk of the drug?

23 A Yes.

24 Q So in, for example, your Tab 3, reference number
25 3, which is an article from the Journal of the

1 American Medical Association in 1988, this was
2 comparing a drug called captopril with digoxin,
3 correct?

4 A Yes.

5 Q And on the page 541 is the Drug Safety and
6 Mortality section, correct?

7 A My, I only, I errored here. I only copied the
8 first two pages, I'm sorry. Can I look at yours
9 then?

10 Q Sure. That's the drug safety section of this
11 particular study, is it not?

12 A So this is in the Results where they're referring
13 to Drug Safety and Mortality; yes.

14 Q And there was some percentage of digoxin toxicity
15 in that study, correct?

16 A They talk about the rate of discontinuation due to
17 adverse drug reactions.

18 Q Would you --

19 A And they say it was 4.2 percent with digoxin.

20 Q Would you assume that the adverse drug reaction in
21 the digoxin group was some form of digoxin
22 toxicity?

23 A I guess it differs on what you mean by toxicity,
24 which I would usually consider to mean a dangerous
25 side effect versus an adverse drug reaction, you

1 know. Even to be more specific, I consider
2 toxicity to be a serious side effect, and an
3 adverse reaction that would cause one to
4 discontinue a drug could be, you know, shall we
5 say, a less than serious effect, meaning one that
6 is not, you know, life threatening or threatening
7 a major change in somebody's health status.

8 For example, you might, you know, stop a
9 drug because it makes you cough, or it gives you a
10 headache, or a patient might report that they
11 think the study drug is giving them a cough or a
12 headache, and then they would say, okay, well,
13 then stop the study drug. I wouldn't consider
14 that a toxicity however, but it might be an
15 adverse reaction causing cessation of the drug.

16 Q So in this particular reference, the
17 discontinuance rate in digoxin of 4.2 percent
18 could be either toxicity, or what you say as an
19 adverse event like nausea or vomiting.

20 A They're, I mean, you would have to review the
21 whole paper again, but they are just saying it is
22 an adverse drug effect, and sometimes they'll
23 actually be more specific and tell you what they
24 are. I don't know if they do in that paper. I
25 don't recall.

1 Q Well, I'm just trying to understand your
2 definition. If a patient was taking digoxin and
3 called you and said, I'm nauseous and I'm
4 vomiting, and you in your mind were convinced that
5 this was from digoxin as opposed to the flu or
6 something else, would you call that an adverse
7 event or toxicity?

8 A So, adverse events is a phrase used specifically
9 for clinical studies, I think. So I would be
10 concerned that the patient was exhibiting a
11 symptom of digoxin toxicity and then look into it
12 further.

13 Q Okay.

14 A That's what I would do.

15 Q And if it was in the midst of a clinical trial,
16 you might just call it an adverse event.

17 A You mean that, clinical trial including digoxin?

18 Q Yes.

19 A If it was in the midst of a clinical trial and the
20 patient called that, I would be concerned for
21 toxicity. We would probably bring the patient in
22 and look into it further with, you know, an
23 evaluation, physical exam, laboratory studies, et
24 cetera, and then decide whether it was -- and then
25 probably would report it as an adverse event to

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1 the head of the investigation.

2 Q Okay. All right. Let's go to your Reference 4,
3 which is this milrinone article in 1989 in the New
4 England Journal of Medicine. The first sentence
5 of the actual body of the article says, "Chronic
6 heart failure is a common progressively
7 debilitating condition with poor prognosis."

8 We talked about this a little bit before,
9 but do you still agree with that statement?

10 MR. MILLER: Objection. Asked and answered.

11 A I think the prognosis has improved since 1989 and
12 it's a pretty vague statement.

13 Q Okay.

14 A You know, in terms of poor.

15 Q How would you characterize the prognosis now, if
16 it's not poor?

17 A It would depend on the setting. I mean, if I was
18 with a patient, I would try to be as optimistic as
19 possible. If I was writing a grant, I would try
20 to be as specific as possible and say that the
21 two-year mortality for Class 2, Class 3 heart
22 failure's approximately 15 percent, and is that --
23 I'd leave it to the reader to decide whether that
24 was good, poor or whatever.

25 Q Page 679 is the Adverse Drug Effects section of

1 this article?

2 A Okay.

3 Q And at the next page, they talk about the
4 discontinuance rates. There were discontinuances
5 for digoxin, were there not?

6 A Let's see.

7 Q It's in the last sentence of the section.

8 A I'm still in the middle of the section. So I'm
9 sorry, ask your question again. I just needed to
10 review the study in my mind.

11 Q Were there discontinuances of digoxin in the
12 study?

13 A It's hard to say because there was, in this
14 sentence, they say there were a group of patients
15 that were receiving either dig or diuretic, and
16 they say here that, "Adverse effects prompted
17 discontinuation of milrinone in 10 of 119 patients
18 as compared with 2 of 111 who were receiving
19 either dig or diuretic." So they're talking about
20 discontinuation of milrinone. They're talking
21 here about discontinuation of milrinone.

22 Q Is what you're telling me, you can't tell whether
23 the 2 discontinuances were digoxin or whether it
24 was a diuretic?

25 A I think that the 2 is referring to discontinuation

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1 of milrinone because remember, there was a
2 treatment, an arm of this study was this
3 combination arm where patients could receive
4 milrinone in addition to dig or diuretic, or on
5 its own, and I think what they're telling us here
6 is about how often milrinone was discontinued.

7 Q Got you. All right. Let's go to the last page of
8 the article. The very last sentence says, "Our
9 results in patients already receiving digoxin
10 suggest however that no clinical benefit would be
11 derived from either the substitution of milrinone
12 for digoxin or the addition of milrinone to
13 digoxin treatment."

14 First of all, did I read that correctly?

15 A I believe you did.

16 Q Was that still true in 2009, 10 years after this
17 was published?

18 A In this patient population of outpatient use of
19 treatment with chronic heart failure, that adding
20 or substituting milrinone for dig, oral milrinone
21 for dig, may be true. I mean oral milrinone is
22 not available.

23 Q Okay.

24 A So for this group of patients, in a situation for
25 which milrinone is not currently available, it's

1 hard to say.

2 Q Okay.

3 A I'm not sure I understand your question.

4 Q In 2009, was IV milrinone beneficial either
5 substituted for or in place of digoxin treatment?

6 A I think there are situations where it would be,
7 yes.

8 Q All right.

9 A Its use would be very different than the goals of
10 this study.

11 Q Do the elderly tend to take more drugs than
12 younger patients?

13 MR. MILLER: Object to form.

14 MR. MORIARTY: What's the objection? What's
15 the matter with the form of that?

16 MR. MILLER: I think it's vague, Matt.

17 MR. MORIARTY: Vague isn't a form.

18 Q Go ahead. You can answer.

19 A My understanding is that in general, the elderly
20 receive more medications than younger patients.

21 Q And that's called poly pharmacy?

22 A Well, I think poly pharmacy is anybody taking more
23 than one drug.

24 Q All right. And is the population of elderly
25 patients on, taking multiple drugs, at increased

1 risk for adverse drug events?

2 A I don't know. I don't know enough about that type
3 of statistics or research.

4 Q Are you familiar with any statistics on what drugs
5 in that population lead to the highest rates of
6 adverse drug events?

7 A I'm not.

8 Q Do patients with heart failure frequently have
9 impaired renal function?

10 A They often do, yes.

11 Q Do you know whether or not cardiac glycoside
12 toxicity is one of the most frequent adverse drug
13 reactions encountered in the elderly?

14 A I don't know.

15 Q So along those lines, in a paper published by
16 Kristin Williamson in the Archives of Internal
17 Medicine in 1998, she says that, "Digoxin is one
18 of the most frequently prescribed medications and
19 has historically been implicated as one of the
20 most common causes of adverse drug reactions." Do
21 you have any basis to disagree with her on that?

22 A I can't really agree or disagree. It's -- I'd
23 need to see the evidence behind the statement.

24 Q She also says, "Therapeutic drug monitoring
25 improves patient care and likely contributes to

1 the suspected decrease in digoxin toxicity.

2 However, elevated concentrations alone do not
3 constitute toxicity."

4 Do you agree that elevated concentrations
5 alone do not constitute toxicity?

6 A No, I disagree with that. I think that there are
7 certain levels, and I think I put it in my report
8 which, that is toxic, and even certain levels that
9 I would treat absent symptoms.

10 Q All right. Let's assume that a patient has a
11 level of 2.2. Let's keep it fairly simple and
12 close to 2 nanograms per milliliter. You wouldn't
13 say that just because a patient has a serum
14 digoxin concentration of 2.2, that they have
15 digoxin toxicity, would you?

16 A I would say that they have a plasma level that,
17 you know, if it represents the steady state,
18 plasma concentration is associated with toxicity,
19 and I would be concerned that some action be taken
20 to prevent some of the manifestations of digoxin
21 toxicity that can occur in the absence of
22 preceding signs and symptoms.

23 We sort of talked earlier that yes, I do
24 think that toxic arrhythmias can occur, and I've
25 seen them occur in the absence of preceding signs

1 and symptoms, and if that was a -- with that
2 level, I would be concerned that digoxin toxicity
3 either can occur or is occurring.

4 Q I understand what you're saying, that you would be
5 concerned, but that wouldn't necessarily spur you
6 to write in the diagnosis section of the chart,
7 "digoxin toxicity," without more information than
8 just a serum digoxin concentration.

9 A I might say, toxic level of digoxin; that's what I
10 would say is occurring.

11 Q Well, is digoxin toxicity really a diagnosis where
12 you're blending the clinical, the
13 electrocardiographic and the laboratory together?

14 A I think it can be, yes. I think almost all of our
15 diagnoses are. But it can be a diagnosis based on
16 level alone.

17 Q When you have patients on digoxin, do you target a
18 particular range of serum digoxin concentration?

19 A If it's for the heart failure indication, yes, I
20 do.

21 Q And what is your target range?

22 A I follow the recent guidelines of aiming between
23 approximately .5 and .8 nanograms per ml.

24 Q Do you routinely order serum digoxin
25 concentrations in your patients?

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1 A Yes.

2 Q Do you order them just for monitoring, or do you
3 only order them when they are symptomatic?

4 A Just for monitoring or when they are symptomatic.

5 Q All right. Is there some frequency with which you
6 try to do it for monitoring purposes?

7 A I try to monitor them approximately twice a year,
8 more so if I think there is anything that could
9 possibly be affecting their level.

10 Q Did you ever practice with a doctor, Thomas W.
11 Smith, who at least back in the '80s was at the
12 Brigham and Women's Hospital here in Boston?

13 A No.

14 Q All right. He published an article in the Journal
15 of the American Academy of Cardiology. I don't
16 think I said that right, the JACC.

17 A American College of Cardiology.

18 Q American College. It said, at page 47, "In terms
19 of the management of the individual patients, I
20 would emphasize that no specific serum
21 concentration exists that can be used to define a
22 clear boundary between the presence and absence of
23 toxicity."

24 Do you agree with him on that?

25 MR. MILLER: Matt, I'm going to object to

1 the reading from a document we don't give the
2 doctor a chance to read it first here.

3 MR. MORIARTY: Okay. I just asked if he
4 agreed with the statement. He is an adult and he
5 is very smart. He can ask for the article if he
6 wants it, Pete.

7 MR. MILLER: I'm objecting then, and I can
8 do that if I want to.

9 MR. MORIARTY: Yes, you can.

10 Q Do you want to see it, doctor?

11 A Yes, I do want to see the article. I think it
12 would be appropriate. And thanks for saying that
13 I'm very smart. I'll tell my daughters.

14 Q I understand the problem.

15 This is the article and the, what I'm
16 referring to is back here, not on the purple flag
17 page, but it is a highlighted statement, okay.

18 A I think I would disagree with that, and I would,
19 and Dr. Smith is or was much smarter than I am,
20 but this was written 25 years ago, before a lot of
21 the studies of digoxin and digoxin toxicity came
22 out, and actually, before many of the current more
23 precise assays came out.

24 So I mean, I knew Dr. Smith. He was an
25 incredible clinician and an incredibly smart

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1 person, but I would disagree with that statement
2 as it applies in the more recent era.

3 Q Okay. Have you ever made a report to the FDA of
4 an adverse drug reaction?

5 A Yes.

6 Q Outside the confines of a clinical trial, have you
7 ever made a report to the FDA of an adverse drug
8 reaction?

9 A Yes. And it was, it was recent.

10 Q What was the drug?

11 A It was Sildenafil.

12 Q Have you ever made an adverse event report to the
13 FDA regarding a cardiac glycoside?

14 A No.

15 Q Are you aware of any medical literature which says
16 that digoxin causes or contributes to renal
17 failure?

18 A I am not aware of that, no.

19 Q Can we go back to your reference number 1, please.
20 At page 2962, and this is that Kirkwood Adams
21 article, isn't it?

22 A Yes. Gheorghiade and Adams.

23 Q Tell me one more time how to pronounce his name?

24 A When I speak, I usually call him Mihai.

25 Q Mihai?

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1 A Gheorghade.

2 Q Gheorghade.

3 A He's Romanian.

4 Q Mihai Gheorghade and Kirkwood Adams, your
5 Reference 1.

6 A Yes, and Bill Colucci.

7 Q Page 2962, first column is, starts out by talking
8 about women, correct?

9 A Yes.

10 Q And the last sentence says, "For now, it is
11 prudent to administer low doses of digoxin only in
12 women with heart failures with very low left
13 ventricular injection fractions and symptoms that
14 occur with minimal exertion or at rest despite
15 standard therapy;" correct?

16 A That's the opinion of the authors, yes.

17 Q And what they're talking about is basically women
18 with, it can be given in women with advanced heart
19 failure who have very low ejection fractions and
20 symptoms, right?

21 A They're saying that that's when it's prudent to
22 administer the agent.

23 Q Can you go to your Tab 5, or your Reference 5,
24 please. It's the 2009 guidelines.

25 A Yes.

1 Q And I'd like you to go to, these are kind of oddly
2 numbered, but there is a page called e7 relatively
3 early in this paper, do you see that?

4 A Got it.

5 Q The first paragraph under Definition of Heart
6 Failure, says, "The cardinal manifestations of
7 heart failure are dyspnea and fatigue, which may
8 limit exercise tolerance," and then it goes on to
9 mention fluid retention and some other things; do
10 you see that?

11 A Yes.

12 Q Can patients who are in, who have heart failure
13 still have shortness of breath and fatigue when
14 treated appropriately?

15 A Yes.

16 Q If you go now to page e27, bottom right-hand
17 corner, they're talking about a class of drugs
18 called angiotensin suppressors, right?

19 A Angiotensin converting enzyme inhibitors.

20 Q ACE inhibitors for short, right?

21 A Yes.

22 Q And they're talking about adverse effects of these
23 kind of drugs; right?

24 A Yes.

25 Q And they say, "The most common adverse effects of

1 ACE inhibition in patients with heart failure are
2 hypotension and dizziness," is that right?

3 A That is what they say, yes.

4 Q Are ACE inhibitors commonly given in conjunction
5 with digoxin in heart failure patients?

6 A Yes.

7 Q And hypotension and dizziness are potential signs
8 or symptoms of both problems with digoxin or ACE
9 inhibitors, correct?

10 A Yes. I think that the mechanism by which the
11 agents cause those symptoms differ, and they are
12 usually discernible by, you know, reviewing the
13 specific situation.

14 Q Okay. All right. Let's go to e33, please.
15 Bottom of the left column is talking about beta
16 blockers, is it not?

17 A Yeah, this is the beta blocker section.

18 Q And it says the beta blockers can produce
19 hypotension, but, which is usually asymptomatic,
20 but may produce dizziness, light-headedness or
21 blurred vision; do you see that?

22 A Yes.

23 Q Are those also potential signs or symptoms of
24 digoxin problems?

25 A They are. But again, the mechanisms can differ

1 and can usually be differentiated in an individual
2 situation.

3 Q E34, please.

4 A Yes.

5 Q Very bottom left column, it says, "There has been
6 no prospective randomized evaluation of the
7 relative efficacy or safety of different plasma
8 concentrations of digoxin;" do you see that?

9 A Yes.

10 Q Is that, do you agree with that?

11 A I agree, yes.

12 Q The studies that, a lot of the studies we've been
13 talking about today, including Mihai Gheorghide,
14 Kirkwood Adams and others are retrospective
15 studies, are they not?

16 A Well, they're a review article. They're not even
17 a study. They're just reviewing other studies. I
18 mean, we talked about the DIG study, for example,
19 the DIG captopril study and the DIG milrinone
20 studies. They're studies.

21 Q Right-hand column, about two-thirds of the way
22 down, sentence says, "In addition, a low lean body
23 mass and impaired renal function can also elevate
24 serum digoxin levels which may explain the
25 increased risk of digitalis toxicity in elderly

1 patients;" do you agree with that?

2 A Yes, those are certainly considerations when
3 assessing the risk of digoxin toxicity.

4 Q Next sentence says, "Of note, one analysis
5 suggested that women may not benefit from digoxin
6 therapy and may be at increased risk for death
7 with such therapy."

8 Do you agree with that?

9 A I don't. I mean, I'd want to again review the
10 study they're referencing, reference 379. It was
11 a retrospective study, as I recall, and I'd want
12 to review that study before saying I'd agree or
13 disagree.

14 Q Rathore's article, which is cite 379, is a
15 retrospective of analysis in the DIG study, isn't
16 it?

17 A Again, I'd want to review it.

18 Q I have the wrong Rathore article. Sorry, I can't
19 help you there.

20 All right, let's go to page e58, will be the
21 last thing I'm going to ask you about this
22 document. E58, first column, under section 6.2,
23 Noncardiovascular Disorders, it says, "Patients
24 with heart failure frequently have impaired renal
25 function as a result of poor renal perfusion,

1 intrinsic renal disease or drugs used to treat
2 heart failure. Patients with renal hypoperfusion
3 or intrinsic renal disease showed an impaired
4 response to diuretics and ACE inhibitors, and are
5 at increased risk of adverse effects during
6 treatment with digitalis."

7 Do you agree with all of that?

8 A Yes.

9 Q There is a quote attributed to a Greek named
10 Paracelsus that says, "The dose makes the poison;"
11 do you agree with that.

12 A I don't know what he is referring to, I'm sorry.

13 Q Okay. In your own --

14 A Can we just take a moment here to stop?

15 Q Can I just finish asking you about Paracelsus?

16 A Sure. Yes. Go ahead. Of course.

17 Q When you do your own clinical trials, or when
18 you're seeing patients clinically, sometimes they
19 will have adverse effects from medications they
20 are taking, is that correct?

21 A Yes.

22 Q And if you can, what you want to know is the dose
23 of the medication they are taking; is that one
24 thing you want to know?

25 A Sorry, what's the goal? Rephrase.

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1 Q To figure out if the medication may be causing the
2 illness or the adverse effect.

3 A Okay. All right.

4 Q You'd want to know the dose of the drug; correct?

5 A You'd want to know the dose, yes; I think that
6 would be helpful.

7 Q You want to know how frequently they're taking
8 that dose, correct?

9 A Right.

10 Q Because almost anything, including water, can be
11 toxic if you take enough of it, right?

12 A I would agree with that.

13 Q All right. So what Paracelsus I assume is saying
14 is the dose is an important thing to know when
15 figuring out whether something is poisonous.

16 A I think it's among many factors, yes.

17 Q So you'd want to know dose and duration, among
18 other factors?

19 A Among other factors, yes.

20 Q Now we can take a break.

21 A I just wanted to sort of evaluate where we were.
22 It's one o'clock. I wanted to look at my own
23 schedule and see.

24 Q Why don't you do that.

25 (Off the record.)

1 MR. MORIARTY: Can you mark that one,
2 please.

3 Mark it as 43(B).

4 (Article: Relationships of Serum Digoxin
5 Concentration to Mortality and Morbidity
6 in Women in the Digitalis Investigation
7 Group Trial marked Defendant Exhibit
8 No. 43(B) for identification.)

9 Q Okay. I'm going to give you the Exhibit version.
10 This is 43(B). You can give that version to
11 Mr. Miller. This article from the Journal of the
12 American College of Cardiology was published in
13 2005; is that correct?

14 A Yes.

15 Q And the lead author is Kirkwood Adams, is that
16 right?

17 A Yes.

18 Q Have you seen this article before?

19 A I may have. I don't immediately remember it.

20 Q I've got some very specific questions about it for
21 you. In the Results section of the little
22 abstract at the outset of the article, it says,
23 "In contrast, SDC's from 1.2 to 2.0 nanograms per
24 milliliter were associated with an HR," which I
25 assume means hazard ratio, "for death for women of

1 1.33." And then it gives the confidential
2 interval in the parentheses, is that right?

3 A That is correct.

4 Q First, tell me your understanding of how you would
5 translate a hazard ratio into either a percentage
6 or some way to commonly say increased level of
7 risk.

8 A Well, I think that the risk here, what they're
9 trying to say is the risk on the average -- well,
10 in general, it tells you the risk relative to
11 unity of a certain event happening.

12 Q I didn't understand that. If for example, if I
13 want to talk as a common layman about increased
14 level of risk, I would say, we've doubled the
15 risk, or we've increased the risk 25 percent or
16 something along those lines.

17 A So if you double the risk, that would be a hazard
18 ratio of 2.

19 Q Okay. So what they're saying is that the hazard
20 ratio for women in this serum digoxin
21 concentration range is only 30 percent higher, is
22 that right?

23 A In this retrospective analysis of a study done for
24 a different reason, that, and again, I don't know
25 what -- I don't know how often they were checking,

1 I don't remember, I can go back and look, how
2 often they were checking levels in the DIG trial,
3 and when the levels they're referring to are
4 relative to when the death occurred, but they're
5 saying that the hazard ratio for death for this
6 retrospective analysis for women was 1.33 if they
7 had a serum digoxin concentration in that range.

8 Q Okay. So, and it is a range. It's 1.2 to 2.0,
9 correct?

10 A Um hmm.

11 Q If, from your understanding of the way these are
12 done, and your knowledge of how they work, if you
13 were to actually break it down by serum level,
14 1.2, 1.3, versus 1.9 or 2.0, would you reasonably
15 expect the hazard ratio to be lower at 1.2 or 1.3
16 than it would be at 1.9 or 2.0?

17 A We have no information to answer that question.

18 Q Well, we don't have any information to answer it
19 about this particular study, but is that a
20 reasonable expectation?

21 A Depends on the situation. I mean, we could be
22 very flat in that range or not. I don't know.

23 Q That's fine.

24 A Just to, in terms, we usually view these types of
25 retrospective analyses as what we call hypothesis

1 generating, and it would be terrific to now do a
2 prospective trial saying you're going to take
3 women, and you're going to target serum digoxin
4 concentrations for less than 1.2, 1.2 to 2, or you
5 might choose different ranges, and let's do a
6 prospective study where we randomly assign
7 patients to different treatment arms with that
8 goal.

9 We don't know, perhaps there were other
10 factors in this women that had this DIG level
11 compared to other DIG levels that also affected
12 their risk of mortality. This is hypothesis
13 generating. I don't think that we can use it to
14 draw any clinical conclusions from it.

15 Q Are you saying, what you're saying is hypothesis
16 generating, or are you saying this passage I've
17 been asking you about is hypothesis generating?

18 A I'm saying that the passage that you're, you read
19 would lead one not to draw any conclusions from
20 it, but to generate a hypothesis --

21 Q I got you.

22 A -- about digoxin levels in women.

23 Q So you do not draw clinical conclusions from this
24 statement.

25 A I do not.

1 Q All right. Let's go to the second page of this,
2 which is page 498. And again, this is more of a
3 question about how doctors reporting these things
4 frame their terminology. In the upper right-hand
5 corner in the section called: Study Population.

6 A Yes?

7 Q You see that? "A total of 6,738 of the 6,800
8 patients enrolled in the main trial survived for
9 at least four weeks of follow-up." So when you do
10 a study like this, do you define what survivorship
11 is going to be?

12 A I don't understand your question.

13 Q Sure. Well, if you're going to talk about -- I
14 realize this is a retrospective study, but when
15 you do a study and you're going to study end
16 points like mortality, do you generally have to
17 come up with a time frame for the mortality?

18 In other words, if they die within a month,
19 were they included; if they die in three months,
20 they're not?

21 A Generally, you -- I mean, it depends. In the
22 studies that I've designed or participated in, we
23 usually begin assessing survival at the beginning
24 of a patient's entry into the trial.

25 Q Okay.

1 A So, and then we say, we're going to follow the
2 patients for as long as we say the study is going
3 to be, and depends a lot on what we're looking at.
4 I mean, we might say we're going to design the
5 trial to follow patients until a certain number of
6 events have occurred. We might say we're going to
7 follow patients for three years, or three months,
8 or even as we did in the trial that I wrote
9 earlier that you discussed, we followed them for
10 12 weeks.

11 Q But do you ascribe any significance to -- if you
12 were reading this article, what significance would
13 you attach to the statement where they say that
14 these people survived for at least four weeks;
15 assuming they thought it was significant or they
16 wouldn't have written it.

17 A True.

18 We'd really have to go back to the study
19 design trial and see why they, why they make this
20 statement. I don't know why. I'd have to review,
21 you know, this paper. They reference the, I think
22 it's, Reference 7 is their study design paper?
23 Let's see. Well, that's the study itself. That
24 was the DIG study from 1997, and see, you know,
25 exactly why they do this.

1 They are only assessing patients that
2 survived for that four-week period. They go on to
3 the next sentence to limit themselves; so that's
4 6738.

5 Q Got you. Let's go to page 501. Says, I'm sorry,
6 right-hand column, about four sentences down, "In
7 contrast, the risk for mortality was greater than
8 placebo when serum concentrations were greater
9 than or equal to 1.2 nanograms per milliliter, and
10 there was no reduction in the risk of the combined
11 end point at higher serum concentrations."

12 What do you understand that to mean?

13 A There again, you know, as we discussed a few
14 moments ago, that the hazard ratio for mortality
15 in the patients taking, in the patients taking
16 digoxin who -- actually, I wouldn't even step back
17 because we talked about the crossover problem in
18 the study, but in the patients at least that were
19 randomized to digoxin, who had serum digoxin
20 concentrations greater than 1.2, mortality was
21 greater than in those that were on placebo, and
22 their combined end point was, as I recall -- let
23 me go back and look. I've got to read the thing.

24 Q You know what, let me withdraw the question.

25 A Okay, because I don't know what the end point

1 they're referring to there.

2 Q That's too detailed a point for my time. But it
3 says here, "Our study cannot define the mechanisms
4 responsible for the adverse effect of higher serum
5 digoxin concentrations;" do you see that
6 statement?

7 A I do see that.

8 Q Is that consistent with your knowledge of the
9 subject?

10 A That this study does not define the mechanisms
11 responsible, right. I mean, and I think it's also
12 consistent with what I said a few moments ago
13 about this conclusion being hypothesis generating.
14 We need to learn more about, you know, that group,
15 and what their characteristics would have been
16 that might have contributed to higher mortality.

17 Q Okay. So let's go to page 503.

18 A And that the problem, even when we've done that,
19 is that we may not have well-defined all those
20 characteristics, which is why we should do a
21 prospective trial.

22 Q Page 503.

23 A Oh, oh. Can we take a break?

24 Q Do you need to take a break to answer a page?

25 A Yes.

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1 Q Go ahead.

2 (Off the record.)

3 (Document: Facts and Myths about Generic
4 Drugs marked Defendant Exhibit No. 38 for
5 identification.)

6 Q So we were in the middle of some final questions
7 about the Kirkwood Adams article from 2005 which
8 is an Exhibit here.

9 A Right.

10 Q Go to page 503.

11 A 503, yes.

12 Q Left side.

13 A Yes.

14 Q I'm sorry, it starts at 502, the last sentence on
15 502.

16 A Yes.

17 Q "As with any retrospective, nonrandomized study,
18 well-known factors could have confounded our
19 results;" do you see that?

20 A Yes.

21 Q Do you agree that that's a possibility?

22 A Yes.

23 Q And then later, it says, in the same column,
24 "Worse outcomes in patients with high serum
25 digoxin concentrations could be related to

1 underlying renal disease or more severe clinical
2 heart failure;" do you see that?

3 A Yes.

4 Q Do you agree with them?

5 A I think that's speculation. I think those are
6 among the possibilities.

7 Q All right. We've talked --

8 A I guess, just to elaborate for a second, I think,
9 I don't know -- this is in the discussion section,
10 it's not in the results, so this is where the
11 authors are discussing their results.

12 I think that what I would interpret that to
13 mean is that underlying renal disease or more
14 severe heart failure could be leading to higher
15 mortality in these patients, and that it's not
16 clear what the relevance of the digoxin levels
17 are.

18 Q Well, if a doctor was putting a lot of faith in
19 this kind of article and was concerned about a
20 serum digoxin level of 1.2 in a woman with heart
21 failure, the appropriate thing to do would be to
22 discontinue the drug, isn't that true?

23 A No. They might -- I mean, you said they're
24 concerned about it. They might reduce the dose.
25 They might evaluate the risk benefit, as we said

1 earlier, or they might discontinue it. I think
2 there are a number of options.

3 Q Well, if somebody was so impressed by this
4 article, they thought that 1.2 was toxic in a
5 patient of theirs, the appropriate thing to do
6 would be to discontinue the drug.

7 A If somebody thought their patient was toxic, they
8 should certainly hold the administration of the
9 drug.

10 Q You've talked a little bit today or a lot today,
11 about individualizing patients, correct, how each
12 patient is a little bit different?

13 A Each patient is different, yes.

14 Q If a patient was prescribed 125 micrograms of
15 digoxin a day, but took accidentally 250
16 micrograms a day, once, is it possible that they
17 would have no adverse effects at all?

18 A It is possible.

19 Q And if a patient who was prescribed 125 micrograms
20 a day accidentally took 250 micrograms a day, and
21 wound up a week later being toxic, digoxin toxic,
22 would you want to know how many times they took
23 that 250 micrograms a day?

24 A Well, the fact of the matter is they're digoxin
25 toxic. So it might be interesting to know how

1 many times they took it, but there are other
2 factors I would want to know about too, and in
3 terms of treating the patient, they're digoxin
4 toxic.

5 Q Sure. Probably wouldn't make a difference if your
6 only thought was to treat the patient; right?

7 A For the acute treatment, yes. I mean --

8 Q Okay. But if you really wanted to dig into how
9 did the drug cause this toxicity, getting back to
10 what we talked about before, you'd want to know
11 dose and how many times they took that dose to get
12 toxic, wouldn't you.

13 A I think that would be helpful, but it's, you know,
14 it's one factor, and it's, there are so many
15 factors relating to dig absorption and excretion
16 that it's not the most, it's not the only
17 definitive factor there.

18 Q Okay.

19 All right. I'm going to pass you over to
20 Ericka, and while she's questioning I'm going to
21 make sure that we've got everything cleaned up
22 that I need to ask with my notes and these
23 Exhibits, okay?

24 A Okay.

25 Q And if you have any Exhibits, I need to have them

1 back so that you don't accidentally take them to
2 your office.

3 A Here is this. These are considered mine, but I
4 think this is yours. It's not labeled as an
5 Exhibit per se.

6 Q Actually it is, 8. Can't read it.

7 CROSS-EXAMINATION

8 BY MS. DOWNIE:

9 Q I'm going to be skipping around a little bit, so
10 bear with me. I have just some follow-up
11 questions to clarify some points you made in your
12 testimony earlier today.

13 You were talking earlier about the two cases
14 that were sent to you by the Motley Rice firm, and
15 I believe you indicated that Carmen Scott had sent
16 them to you.

17 A Yes.

18 Q And I believe you testified you couldn't recall
19 the specifics of them, but you called them, you
20 did at one point use the phrase, unusual case, an
21 unusual digoxin case.

22 A I don't recall.

23 Q I wrote it down when you said it, so that's why I
24 wanted to ask you if you recall what you may have
25 meant by an unusual case.

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1 A I don't recall saying that, or maybe I misspoke if
2 I did. I don't know if it's possible to go back
3 to the record.

4 Q If it doesn't ring a bell with you, that's fine.
5 I just wanted to see if as time went on, if you
6 recalled any more regarding the specifics of those
7 cases.

8 A I don't.

9 Q Okay. Fair enough.

10 Mr. Moriarty asked you earlier whether or
11 not you were aware of, if Mass. General kept any
12 statistics to determine whether or not there were
13 any spikes in complaints related to digoxin
14 toxicity, and I believe your testimony was you
15 were not aware, but I wanted to ask --

16 A Not whether they kept the statistics.

17 Q That is correct. But I wanted to ask you whether
18 or not in your clinical practice, whether or not
19 at any time you've personally noticed any spike in
20 digoxin toxicity being reported to you by your
21 patients.

22 A No, I'm not aware of that.

23 Q Mr. Moriarty asked you earlier whether or not you
24 had ever prescribed the .50 dose or 500 dose of
25 digoxin; I believe your testimony was that you had

1 not on a chronic basis.

2 A Correct.

3 Q Have you prescribed that amount on any other
4 basis?

5 A When we're loading a patient with digoxin, we
6 might begin, I have given that dose to somebody
7 who had not previously been taking digoxin for a
8 single dose.

9 Q Okay. So would they receive that dosage only one
10 time?

11 A Correct.

12 Q Maybe you could explain to me how it would work.
13 That might be easier.

14 A They would receive that dosage only one time.

15 Q Okay. And then it would go to either 250 or 125?

16 A They might receive another dosage of 250, say,
17 four hours later. And then they would go to a
18 chronic dose, usually 125.

19 Q Okay. You testified earlier that you would be
20 concerned at a level, for serum, an SCC of 2.2,
21 that the patient was toxic, and you made a point
22 to say that if that 2.2 was at a steady state,
23 that would lead you to become concerned that the
24 patient was potentially suffering from digoxin
25 toxicity. Is it important for you to know whether

1 or not that level is steady state level, and if
2 so, why?

3 A A level of 2.2, yes, because I think if a blood
4 was drawn early after the administration of the
5 dose or the patient took the dose, that that level
6 might indeed not be concerning. But if that level
7 represented a steady state level, then yes, I
8 would be concerned.

9 Q And you may have already testified to this, I
10 apologize if you have, but how long after a dose
11 of Digitek would you want to see that test done to
12 ensure that the level that you were getting as a
13 result would be the steady state level?

14 A Optimally, you know, four to six hours.

15 Q Now, again, I think your testimony was the 2.2
16 would give rise to concern for you that the
17 patient was toxic.

18 A Yes.

19 Q And you would investigate further to determine
20 whether or not that was in fact the case. What
21 type of investigation would you do to make that
22 determination?

23 A Take a history for signs and symptoms of dig
24 toxicity, physical exam, electrocardiogram;
25 perhaps check their electrolytes as well to see if

1 there are any of the things we talked about, or at
2 least I talked about in my statement, any of the
3 factors that might exacerbate digoxin toxic
4 effects at a given level.

5 Q And if the patient had no further symptoms or
6 signs that you've just listed for us, if in fact
7 the only thing that they had was the elevated
8 level, would your conclusion then be that the
9 patient was digoxin toxic?

10 A I think I would conclude that they had a toxic
11 level, and I would decrease the dose.

12 Q And by how much would you decrease the dose?
13 Would you discontinue it or --

14 A I wouldn't dis -- it would be unlikely to
15 discontinue it. I would probably decrease the
16 dose by, depends on the individual situation.
17 It's hard to say.

18 Q Would you do a follow-up SCC?

19 A Yes.

20 Q How soon after the initial draw of the example
21 we've been using, 2.2?

22 A And this is in somebody who had no other signs,
23 symptoms, electrocardiographic rhythm
24 abnormalities?

25 Q That's correct.

1 A Probably do a follow-up level in approximately a
2 week.

3 Q Okay.

4 A One week. Four half lives.

5 Q You wouldn't hospitalize a patient based on a
6 level of 2.2 and no symptoms.

7 A And no signs, and no rhythm abnormalities, and no
8 significant electrolyte abnormalities, I would not
9 as a rule. And no other reason for
10 hospitalization.

11 Q Sure.

12 Have you ever seen a Digitek tablet that you
13 believed to appear to be out of specification in
14 any respect, whether in size, color, weight or
15 anything of that nature?

16 A No.

17 Q Have you ever seen any tests that were performed
18 on Digitek tablets that indicated that their
19 content was out of specification in any respect?

20 A No.

21 Q You testified earlier that there were certain
22 situations where you had personally considered
23 whether or not a tablet might have contained more
24 active ingredient because you had no other working
25 alternative explanation; do you recall that

1 testimony?

2 A Yes.

3 Q How many times has that happened?

4 A It's difficult to say in part because earlier in
5 my career, I think that we, you know, believed
6 that the variability of the amount of active
7 ingredient in the tablets varied to a greater
8 extent than it usually does now. And you know, I
9 would say probably happen maybe 10, I'm guessing
10 now, 10 to 15 times.

11 Q To the best of your ability.

12 A To the best of my ability.

13 Q Can you recall, to the best of your ability, when
14 the last time was that you had that type of
15 situation arise in your practice?

16 A Again, I'm giving a very approximate answer of 7
17 or 8 years ago.

18 Q And do you have any knowledge in, let's start with
19 these situations specifically, but do you have any
20 knowledge regarding what brands of digoxin the
21 patients in those situations were taking?

22 A I don't recall.

23 Q Do you generally have any knowledge regarding the
24 brand of digoxin that your patients are ingesting?

25 A There are times, rarely, when patients will ask

1 that a specific brand be given to them, and then I
2 do. I think it was certainly, if I go back maybe
3 10 or perhaps even a few more years, that we
4 would, because of concerns about variability in
5 the preparations, that would we would specify
6 brand names as a rule.

7 Q What brand names would you specify?

8 A We usually, I don't know whose side you represent,
9 we would usually specify Lanoxin.

10 Q Okay.

11 MR. MORIARTY: We're not insulted.

12 Q Again, I apologize if you've already been asked
13 this, but when is the last patient that you've
14 treated that you believed was digoxin toxic?

15 A Probably about two months ago.

16 Q Can you tell us sort of the circumstances of that
17 patient coming to see you, and what your diagnosis
18 was, and what it was based upon?

19 A It was a patient who was receiving digoxin for
20 rate control of atrial fibrillation that I was
21 helping to take care of, who had a junctional
22 rhythmn, and had a, I think had been receiving too
23 much digoxin, and thought they had digoxin
24 toxicity.

25 Q When you say they were receiving too much digoxin,

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1 do you mean they were taking too much digoxin, or
2 perhaps you can clarify your statement so I
3 understand?

4 A I think they were taking too much digoxin.

5 Q Was this an elderly patient?

6 A Well, they were in their sixties. I'll let you
7 decide.

8 Q I will say nothing more about that.

9 A I know how old you are by definition, so probably.

10 MR. MORIARTY: Very politic.

11 Q Well, then let me ask a better question. When you
12 say they were taking too much digoxin, were they
13 taking more than they were prescribed or did you
14 believe --

15 A No, they were prescribed the dose that I thought
16 was what it should be.

17 Q I see. So what did you do for treatment of the
18 patient?

19 A We held the digoxin for several doses and then
20 resumed at a lower dose.

21 Q As I understand it, you are rendering no opinions
22 in this case as to whether or not a defective
23 digoxin tablet caused an injury in a specific
24 plaintiff.

25 A I haven't been --

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1 Q Is that fair?

2 A I think I was asked to review the two cases thus
3 far. I don't remember what my opinion was. They
4 didn't ask me to write a report. And I've not
5 been asked to do anything since on that.

6 Q Have you been asked to render any opinion
7 regarding whether or not Digitek was manufactured
8 and distributed with any type of defect?

9 A No, I've not been asked to render any kind of
10 opinion related to that.

11 MS. DOWNIE: I think that's -- hold on.

12 In the interest of time, why don't you go
13 ahead if you have some follow-up. I think I'm
14 done but I may have one more pass.

15 REDIRECT EXAMINATION

16 BY MR. MORIARTY:

17 Q Ericka was asking you some questions about the
18 timing of taking a serum digoxin concentration. I
19 want to follow-up on that.

20 A Okay.

21 Q I'm not much of an artist, but if you can
22 conceptualize a dose and response curve, and on
23 the vertical axis it would be the nanograms per
24 milliliter, and on the horizontal axis, time,
25 okay.

1 A Um hmm.

2 Q If a patient is on a dose of, say, 250 micrograms
3 a day at steady state, can there be a time
4 everyday, within the first few hours after they
5 take their dose, when their serum level would show
6 above 2 nanograms per milliliter?

7 A I believe so, yes.

8 Q Okay. So if for some reason we wanted to do a
9 study on a group of people who were taking
10 digoxin, and we drew all the serum digoxin
11 concentrations at 2 or 4 hours, whatever, I leave
12 it to others to figure out when the drug is
13 absorbed and starts to metabolize, but there would
14 be peaks or C max's among that group of people
15 above 2 nanograms per milliliter, correct?

16 A In the serum concentration.

17 Q Yes.

18 A There might be.

19 Q Okay. And that's a temporary number, and then it
20 falls off as you get out to the 6, 8 hours when
21 you really want to measure it, right?

22 A Right.

23 Q So the level does not necessarily cause toxicity
24 in that early time period, and the level has to be
25 taken into context of when it is drawn; correct?

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1 A Well, what causes toxicity is the tissue
2 concentration of digoxin, and my understanding is
3 that early after it's taken, that the plasma level
4 does not necessarily represent the tissue levels.

5 Q I see. Okay. Do you know anything about
6 postmortem redistribution of digoxin?

7 A No.

8 Q Just made that topic about five minutes shorter.

9 MR. MORIARTY: I don't have anything else.

10 MS. DOWNIE: No, no more questions. Thank
11 you.

12 MS. CARTER: Just give us a couple minutes.

13 (Recess taken.)

14 MR. MILLER: Just a couple quick questions
15 and we'll finish this up.

16 MR. MORIARTY: Objection. No, I object. I
17 don't think you should be allowed to ask your own
18 expert questions in my discovery depo.

19 MR. MILLER: Okay. Objection is noted.

20 CROSS-EXAMINATION

21 BY MR. MILLER:

22 Q Doctor, it was pointed out to me, and I'm going to
23 see if you recall, have you had an opportunity to
24 meet an attorney from Motley Rice named Fred
25 Thompson? Do you recall meeting Fred Thompson?

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1 A I don't. I think we spoke on the phone. I don't
2 recall meeting him.

3 Q You've been asked several questions today about
4 your report. Has anything been asked of you that
5 changes any of the opinions in your report?

6 A We found a typo.

7 Q Okay.

8 A That I think was appropriate to correct.

9 Q All right. But other than the typo, nothing has
10 been shown to you or asked of you today that would
11 change any of the opinions in your report.

12 A No.

13 MR. MILLER: That's all the questions I
14 have.

15 MS. CARTER: Could you tell us what the typo
16 was, I missed that?

17 MR. MORIARTY: He has the word most --

18 MS. CARTER: Rather than modest.

19 MR. MORIARTY: And it should be modest.

20 THE WITNESS: I have too much reliance on
21 spell check.

22 MS. CARTER: That's fine. If it's already
23 in the record, then --

24 MR. MORIARTY: It's in the record. We've
25 corrected it.

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1 THE WITNESS: It's on page 5.

2 BY MR. MILLER:

3 Q And on page one, if you take a look at the
4 Mechanisms of Action, and I believe that first
5 sentence where it says, "canine hearts during the
6 1920, that's supposed to be 1920's, right?

7 A Yes, that's 1920's, correct.

8 Q All right. And then the only other one that I saw
9 was, towards the bottom of that paragraph, it
10 should be 1850's instead of 1805?

11 A No, 1950's.

12 Q Oh, 1950's, okay.

13 A You're right. Sorry. Do you want me to submit
14 some sort of revised?

15 Q No, that's quite all right. Those are all the
16 questions I have.

17 MR. MORIARTY: We're done. Do you know
18 about reading and signing?

19 MR. MILLER: He will read and sign. We're
20 not going to waive that.

21 MR. MORIARTY: Okay. We're off the record.

22 (Off the record at 1:55 p.m.)

23

24

25

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C E R T I F I C A T E

COMMONWEALTH OF MASSACHUSETTS

MIDDLESEX, SS.

I, Lisa McDonald Valdario, Registered Professional Reporter and Notary Public, in and for the Commonwealth of Massachusetts, do hereby certify that:

MARC J. SEMIGRAN, M.D., the witness whose deposition is hereinbefore set forth, was duly sworn by me, that I saw a picture identification for him in the form of his MGH ID, and that the foregoing transcript is a true and accurate transcription of my stenotype notes to the best of my knowledge, skill and ability.

I further certify that I am not related to any of the parties in this matter by blood or marriage and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand and notarial seal this 26th day of June, 2010.

Lisa McDonald Valdario, RPR, RMR
Notary Public
My commission expires: June 9, 2011

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